CASE REPORT

Radical Prostatectomy on a 66-year-old Patient with a Positive ^{18}F-PSMA Uptake: Potential Application for Multiple Negative Prostate Biopsy Results

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The decision to proceed with radical prostatectomy has to be supported with biopsy-proven prostate cancer. However, when a patient has persistently multiple negative prostate biopsies and a high PSA, a serious diagnostic and therapeutic dilemma arises. The PIRADS score generated by the multiparametric-MRI of the prostate provides a guide for a template biopsy using MRI-ultrasound fusion technology, with the hope of minimizing a false negative result. Fluorine-18 Prostate-Specific Membrane Antigen (^{18}F-PSMA) PET CT scan, on the other hand, is used mainly for staging prostate cancer after biochemical recurrence. The use of ^{18}F-PSMA PET CT in the primary clinical diagnosis of prostate cancer has never been reported.

The authors performed radical prostatectomy on a 66-year-old HIV-positive male with suspicious lesion on ^{18}F-PSMA, PIRADS 5 on mp-MRI, and a persistently elevated PSA >100 despite multiple negative biopsies. The final histopathological analysis confirmed the presence of adenocarcinoma of the prostate, Gleason 7 (3+4), with negative margins. There were no intraoperative complications, and the patient was discharged in good condition. On follow-up, he had a nadir PSA of 0.058 ng/ml, has partial incontinence, and decreased erectile function and was advised phosphodiesterase inhibitors.

^{18}F-PSMA may be utilized in the decision process for patients who are highly suspected with malignancy but have no preoperatively biopsy-proven cancer after multiple negative biopsies.

Key words: Prostate cancer, Fluorine 18 Prostate Specific Membrane Antigen (^{18}F-PSMA), Positron Emission Tomography (PET), prostate biopsy, radical prostatectomy, negative biopsies

Introduction

Early diagnosis of prostate cancer has been facilitated by PSA testing, followed by a timely core needle biopsy. In order to minimize a false negative result, biopsy strategies were developed such as saturation and lesion-directed core sampling via either an exclusive transrectal ultrasound-guidance or more recently, with MRI-transrectal ultrasound-guided fusion technology.

A diagnostic and therapeutic dilemma exists when a patient has a persistently elevated PSA and yet, has had multiple repeated negative biopsies. This crisis becomes even more problematic when imaging studies such as the mpMRI and ^{18}F-PSMA both suggest the presence of malignancy. To proceed with radical prostatectomy without biopsy-proven cancer in this scenario is not only clinically unjustified but may also be subjected to scrutiny.

Fluorine-18 Prostate-Specific Membrane Antigen (^{18}F-PSMA) targeted Positron Emission Tomography (PET) CT scan is a novel imaging study for clinical staging of prostate cancer and for monitoring after biochemical recurrence.[1] It has never been used for primary diagnosis of prostate cancer. The authors used ^{18}F-PSMA as a guide in recommending radical prostatectomy on a patient with history of multiple negative prostate biopsies.

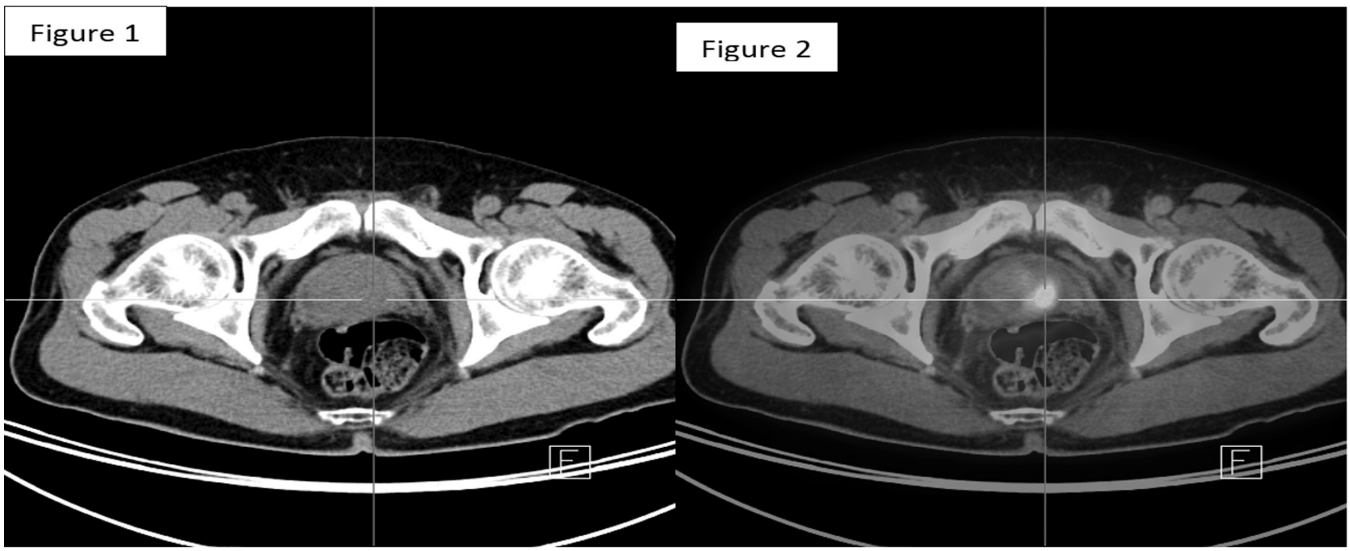
The Case

A 66-year-old hypertensive, HIV-positive male patient presented three years ago with bothersome lower urinary tract symptoms. His medications include Abacavir / Dolutegravir / Lamivudine (Trumeq) and Enalapril which were taken with good compliance. He had a prolonged history of testosterone injections for three years for androgen deficiency and anti-retroviral induced lipodystrophy. Testosterone injectables were then shifted to oral Testosterone Undecanoate (Andriol® testocaps) 40mg/cap thrice a day from May 2016 to October 2016. There was no intake of testoterone afterwards. Patient had no previous surgeries and no familial history of cancer. Initial PSA was 54.12 ng/dL. Transrectal ultrasound-guided biopsy was done revealing benign prostate tissues. Patient was advised observation.

One year later, he had persistent LUTS and the PSA remained elevated at 50 ng/dL. Multiparametric MRI of the prostate showed a prostate volume of 50g, PI-RADS 5 and 3 on the right (2.3cm x 2.9cm x 3.4cm) and left (1.6cm x 1.5cm x 1.2cm) peripheral zones respectively. An 18-core transrectal ultrasound-guided biopsy with special attention on those areas that were considered suspicious for malignancy (cognitive fusion), but still showed a negative result.

After another year, (March 2018), patient consulted at the University of California San Francisco Medical Center. At this time, the PSA was higher at 100 ng/dL. An 18-core transperineal prostate biopsy was done but again showed a negative result. This was followed by an MRI-ultrasound fusion biopsy eight months later (November 2018) but this still showed a negative result.

On July 2019, the patient came back with a moderate IPSS score and the PSA remained elevated >100ng/mL. He was started on dual therapy with tamsulosin and dutasteride. At this point, the authors recommended an ^{18}F-PSMA PET CT scan, which revealed a 61g prostate with a 1.3 cm hypodense focus of moderate FPSMA uptake in the left peripheral zone which was considered to be "likely due to a prostate malignancy." There were no evident PSMA-avid nodal or distant metastases.



Plain (Figure 1) and ^{18}F-PSMA enhanced (Figure 2) views show that the prostate gland is enlarged (61 g) and now has an approximately 1.3 cm hypodense focus of moderate ^{18}F-PSMA uptake (SUV 6.9) in the left peripheral zone. Diffuse mild ^{18}F-PSMA activity is evident throughout the remainder of the prostate. Previously noted lesion in the apex is now seen as an area of homogeneous prostatic parenchyma.

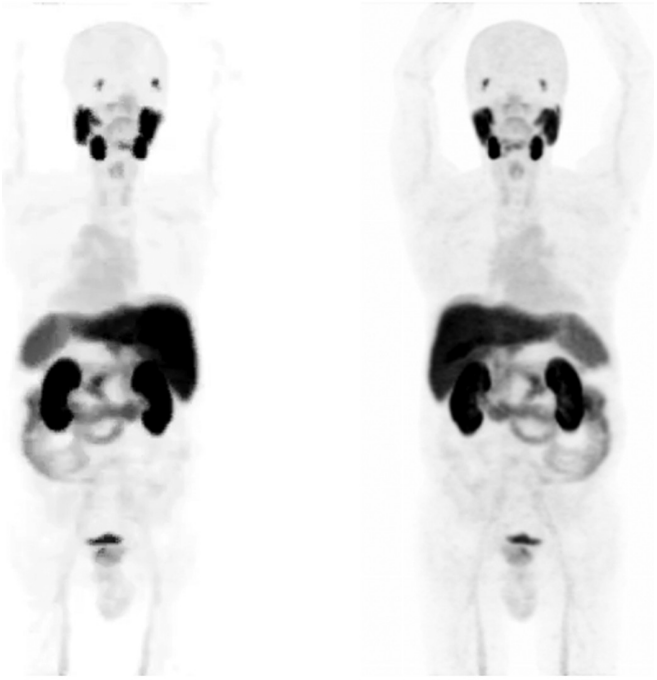


Figure 3: Whole body PSMA PET CT scan showing no evident PSMA-avid nodal or distant metastases.

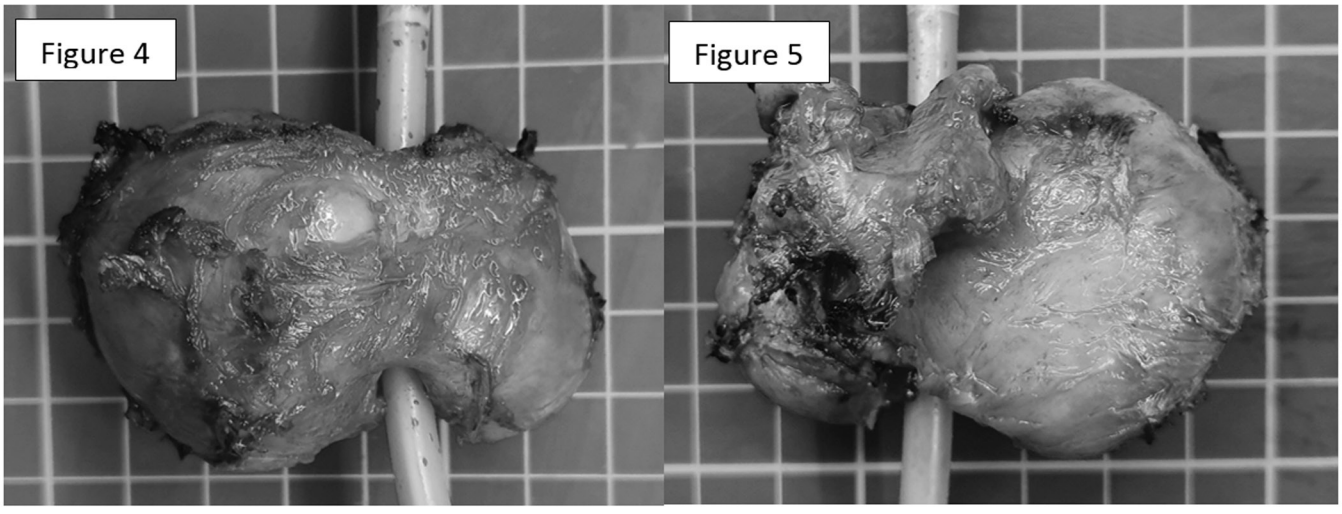
The patient refused to undergo another biopsy given the long history of negative biopsies. He however requested definitive surgical therapy for his bothersome LUTS. Due to the high clinical suspicion of prostate cancer, and in spite of a negative biopsy, the authors decided to recommend open radical prostatectomy, discussing all the risks and benefits of this procedure, and the patient signed an informed consent.

Patient therefore underwent open radical prostatectomy with bilateral pelvic lymph node dissection on September 25, 2019. Intraoperative time was 3 hours with an estimated blood loss of 2100 cc. The rest of the intraoperative and immediate postoperative course was unremarkable. Histopathological analysis showed acinar adenocarcinoma of the prostate with Gleason Score 7 (3+4) Grade Group 2 (2/5) involving less than 5% of the submitted specimen with perineural invasion. There was no extraprostatic extension, seminal vesicle invasion nor lymphovascular invasion was noted. All nine regional lymph nodes were negative for tumor.

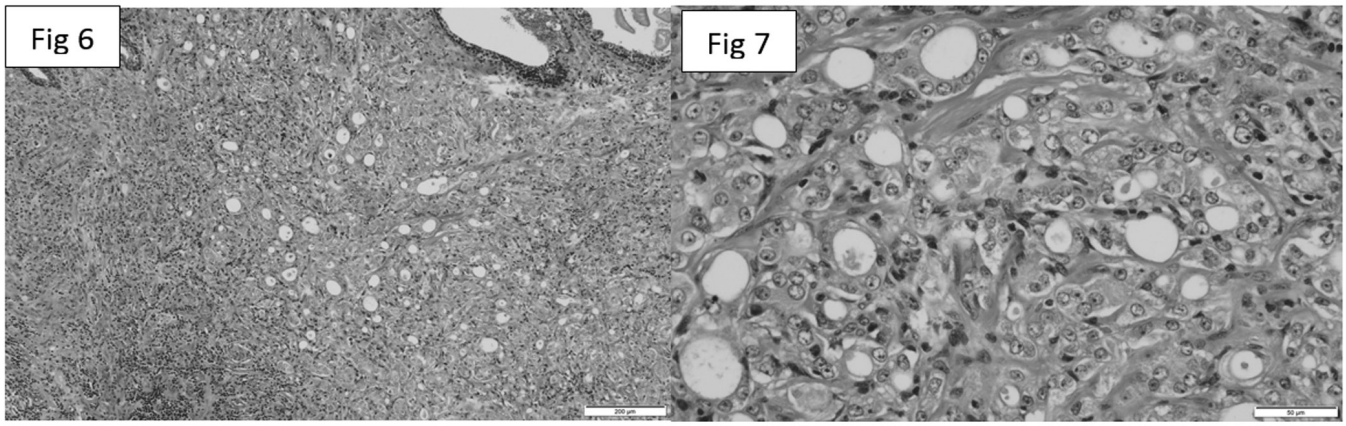
As of writing this report, the patient continues regular follow-up with post-operative partial stress incontinence, which was said to have improved after 5 months. Leaking was said to occur during movement but does not happen while asleep. He has postoperative erectile dysfunction, and patient was advised to take PDE5 inhibitors. Otherwise, patient has no other subjective complaints. PSA as of January 10, 2020 is 0.058.

Discussion

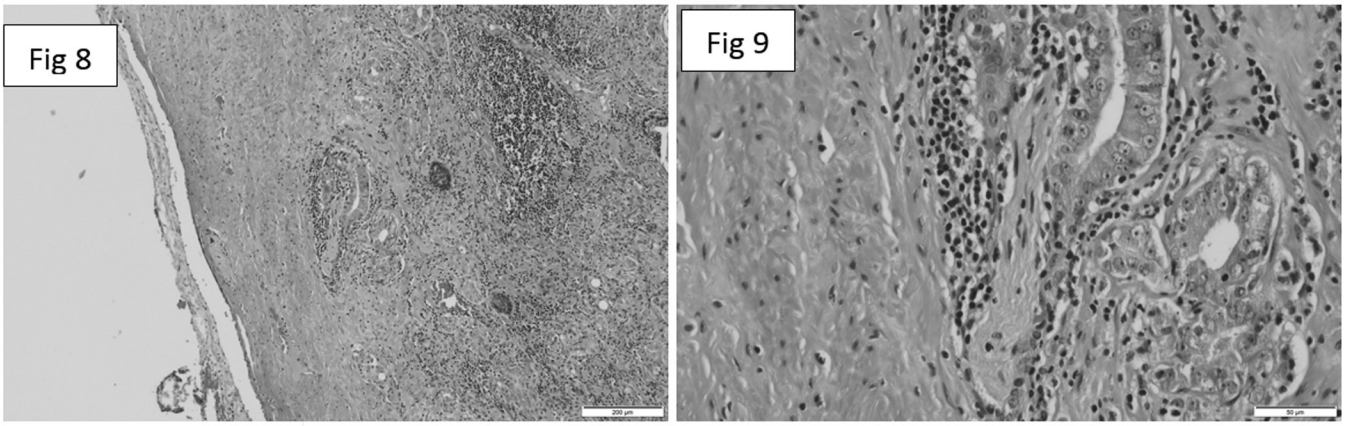
A persistently elevated and rising PSA, together with a high PIRADS score on multiparametric MRI suggests the high likelihood of having prostate malignancy. This should be documented with histological proof of cancer as determined



Figures 4 & 5: Gross specimen of the prostate gland.



Low Power Objective (LPO) (Figure 6) and High Power Objective (HPO) (Figure 7) showing adenocarcinoma of the prostate, Gleason Score 7 (3+4).



LPO (Figure 8) and HPO (Figure 9) images showing presence of perineural invasion.

by a core needle biopsy of the prostate. Based on the most recent NCCN guidelines[2], tissue diagnosis is a "non-negotiable" requirement before recommending radical prostatectomy, which cannot be based solely on a high PSA level. All biopsy strategies and image-guided technology should be utilized to provide a histopathological basis for doing radical surgery.

A urologist reaches a "stalemate" when all biopsies of the prostate reveal negative results in multiple occasions. The increasing PSA of >100ng/ml nonetheless, made us doubt the benign nature of the patient's clinical condition. If the authors were to stratify the patient based on the above parameters and if the patient does have prostate cancer, he will be stratified at the very least as a high-risk disease. Options for therapy will include External Beam Radiation Therapy (EBRT), Brachytherapy or Radical Prostatectomy. However, the first two therapies will not provide them with a tissue to confirm their diagnosis of cancer. If they were just to observe the patient, they would be considerably undertreating the patient given that the patient may have a high-risk disease. Due to a high index of suspicion, the authors had to find another surrogate marker which can support their hypothesis that the patient does have cancer. It is critical that they find this out because it will help guide their planned therapy.

^{18}F-PSMA is a new technology and currently, its role in prostate cancer diagnosis is primarily for restaging and evaluation of biochemical recurrence.[1] However, ^{18}F-PSMA PET CT scan is starting to be used in gaps that the mpMRI could not fill. While

mpMRI is very effective in the detection of clinically significant prostate cancer, it has limited use in the detection and quantification of extraprostatic disease and there is evidence for its promising potential use for primary staging.[3] Another study showed up to 88% sensitivity of ^{18}F-PSMA PET CT especially for high-risk prostate cancer patients.[4] Even though the said study did not recommend the use ^{18}F-PSMA PET CT for initial staging especially for 10% of prostate cancers that do not show PSMA overexpression, ^{18}F-PSMA PET CT is still able to outperform both MRI and CT. For this reason, the authors recommended an ^{18}F-PSMA PET CT scan to give them a clue on their patient's clinical diagnosis.

After a careful and meticulous search of literature, the authors found no patient similar to theirs who had multiple negative biopsies, a rising PSA, and a positive ^{18}F-PSMA test. Therefore, this is the first case report utilizing this imaging modality as a guide for recommending radical prostatectomy.

Multiparametric MRI of the prostate (mpMRI) was initially introduced to identify suspicious areas of the prostate which may then be targeted that may yield significant higher cancer detection rate. The overall sensitivity for predicting positive biopsies was 57-100%, the specificity 44-96% and the accuracy to 67-85%.[5] Later, staging prostate cancer with MRI can detect peripheral zone cancer with a sensitivity of 37-96% and specificity at 50%. This variability made it difficult to resort solely to mpMRI as a guide for determining the presence of cancer. It also cannot be used primarily for recommending radical surgery.

Recently, Keller in 2015 described their experience on two cases of radical prostatectomy on patients with PIRADS 5 lesions on mpMRI but with no preoperative histologic confirmation of malignancy.[6] Final histopathological analysis showed Gleason 7 (4+3) for the first case and Gleason 8 (4+4) for the second case. The present case is somewhat similar to this but the authors hesitated to recommend surgery based on the PIRADS scoring alone because all the four consecutive biopsy strategies persistently showed negative results.

A study done in 2018 comparing results of the different PIRADS lesions and their diagnosis of cancer showed that PIRADS 5 lesions were able to predict PCA in 92% of patients, on their first biopsy, 87% for patients with a previously negative biopsy and 93% on surveillance biopsies.[7] It is notable however that this high predictability of PCA on PIRADS 5 lesions was not validated in the present patient who had a negative fusion biopsy.

Gersman (2013) described patients who underwent transperineal template-guided prostate biopsy with multiple prior negative prostate biopsies with a persistently elevated PSA.[8] Patients had at least 2 negative biopsies with PSA ranging from 5.7 – 68.9. The template-guided biopsy had a detection rate of 50% of prostate cancer wherein Gleason 6 (3+3) was found in 50% of the patients. The patient also underwent a transperineal biopsy, but it resulted to a negative biopsy while having a PSA of >100.

All the negative biopsy experiences of the patient reinforced that biopsy strategies are never guaranteed to generate a higher positive yield. The authors' persistence "to determine the truth" is evident in their repetitive attempts at documenting the presence of malignancy which however failed. A high clinical suspicion was needed to proceed with caution.

It is noteworthy though that even if ^{18}F-PSMA was able to help them diagnose PCA in their patients, they still would not recommend its use for making an initial diagnosis. However, they believe that this case report opens a whole new dimension for its potential use in the primary diagnosis and management of PCA.

Conclusion

In cases where patients present with increasing PSA levels, and a high PIRADS scoring but persistently multiple negative biopsies, ^{18}F-PSMA PET CT could aid in the clinical diagnosis of prostate cancer. Further studies are recommended in order to fully understand and utilize the potential of this imaging modality in similar situations such as the one presented here.

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