



# <sup>18</sup>F-PSMA-1007 PET/CT uptake in multiple angioliipomas caused by PSMA expression in capillaries: a case report

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**Abstract:** Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that was originally cloned in the membrane of prostate gland epithelial cells. It has been confirmed to be highly expressed in prostate cancer cells, and in some non-prostatic tissues, including the brain and some benign lesions. PSMA-based imaging has been extensively used for the assessment of prostate carcinoma. The high uptake of PSMA imaging in these non-prostate cancer lesions may lead to some misdiagnosis. It is of important clinical significance to explore the possible causes of high PSMA uptake in these lesions. Here, we present a case of a 77-year-old man with prostate carcinoma who underwent a whole-body <sup>18</sup>F-PSMA-1007 positron emission tomography/computed tomography (PET/CT) scan for staging. The results of the scan showed intense tracer uptake in both the prostatic bed and in multiple subcutaneous lesions. The subcutaneous lesions were later found to be angioliipomas by histopathological examination. Immunohistochemistry demonstrated strong positive cytoplasmic PSMA staining in lesional prostate cancer cells in prostate carcinoma, and mild-to-moderate positive cytoplasmic capillary PSMA staining in angioliipoma fatty density nodules. Our case report therefore demonstrated that <sup>18</sup>F-PSMA-1007 PET/CT uptake in multiple angioliipomas was caused by PSMA expression in capillaries, and further knowledge of PSMA expression in benign lesions may be critical to minimize false-positive findings with <sup>18</sup>F-PSMA-1007 PET/CT imaging.

**Keywords:** Prostate cancer; prostate specific membrane antigen (PSMA); PET/CT; case report; angioliipoma

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## Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that was originally cloned in the membrane of prostate gland epithelial cells. PSMA expression increases 100–1,000 times in advanced prostate cancer cells, hence the name, PSMA (1). The strong expression of PSMA in prostate cancer is associated with a high serum prostate-specific antigen (PSA) level, high Gleason score, advanced tumor progression, negative prognosis, and has been substantiated as an independent predictor of tumor

recurrence (2), therefore supporting PSMA radioligand-based imaging and therapy for the management of prostate cancer (3). Interestingly, recent studies have reported that PSMA is expressed in other genitourinary malignancies, particularly renal cell carcinoma (4). Enhanced uptake on PSMA-based positron emission tomography/computed tomography (PET/CT) scans have also been ascribed to some benign lesions (e.g., in ganglia or healing rib fractures) (5). There are many reasons for the high expression of PSMA in these lesions. Angioliipoma is a special type of lipoma. It is a rare benign neoplasm which is generally found in subcutaneous tissues. Surgical removal is

possible if necessary, and the final diagnosis is dependent on histopathological evaluation (6,7). Angioliopoma is a special type of lipoma that is formed by mixing mature adipose tissue with hyperactive vascular tissue. In the literature, there are only two reports of angioliopomas as determined by <sup>68</sup>Ga-PSMA and fluorodeoxyglucose (<sup>18</sup>F-FDG) PET/CT (8,9), although the possible reasons for enhanced uptake of PSMA in these angioliopomas are not explained. Herein, we report a rare case of an elderly male patient with multiple angioliopomas, which were detected by <sup>18</sup>F-PSMA1007 PET/CT. Most importantly, we performed a histopathological evaluation and immunohistochemical staining of the angioliopoma lesions and found a possible cause of its high uptake of PSMA. We present the following case in accordance with the CARE reporting checklist (10) (available at <http://dx.doi.org/10.21037/tau-20-1099>).

### Case presentation

A 77-year-old man presented with frequent urination and dysuria which had persisted for 8 months. Physical examination revealed multiple painless nodules distributed subcutaneously in the lower back, upper back, shoulders, and upper arms. There was no palpable lymphadenopathy in the inguinal region. Past medical and family history were unremarkable. The serum PSA level was 27.7 ng/mL. Magnetic resonance imaging (MRI) was followed by a biopsy, which confirmed prostate cancer (Gleason score 8). The patient then underwent a <sup>18</sup>F-PSMA-1007 PET/CT scan for staging. The maximum intensity projection image (MIP) showed intense focal PSMA uptake in the whole enlarged prostate gland, indicating locally advanced prostate cancer (*Figure 1*). Histopathological examination also revealed prostate cancer, as significant PSMA expression in prostate cancer tissue was observed (*Figure 2*). Additionally, the PET/CT scan demonstrated multiple PSMA-avid subcutaneous fatty density nodules (*Figure 1E,F,G*), which had spread over the areas mentioned above. The highest level of uptake occurred in the nodules of the right lower back, with a SUVmax value of 8.2. The patient underwent radical prostatectomy 3 days after the scan, and 3 lesions (bilateral back and left forearm) were excised.

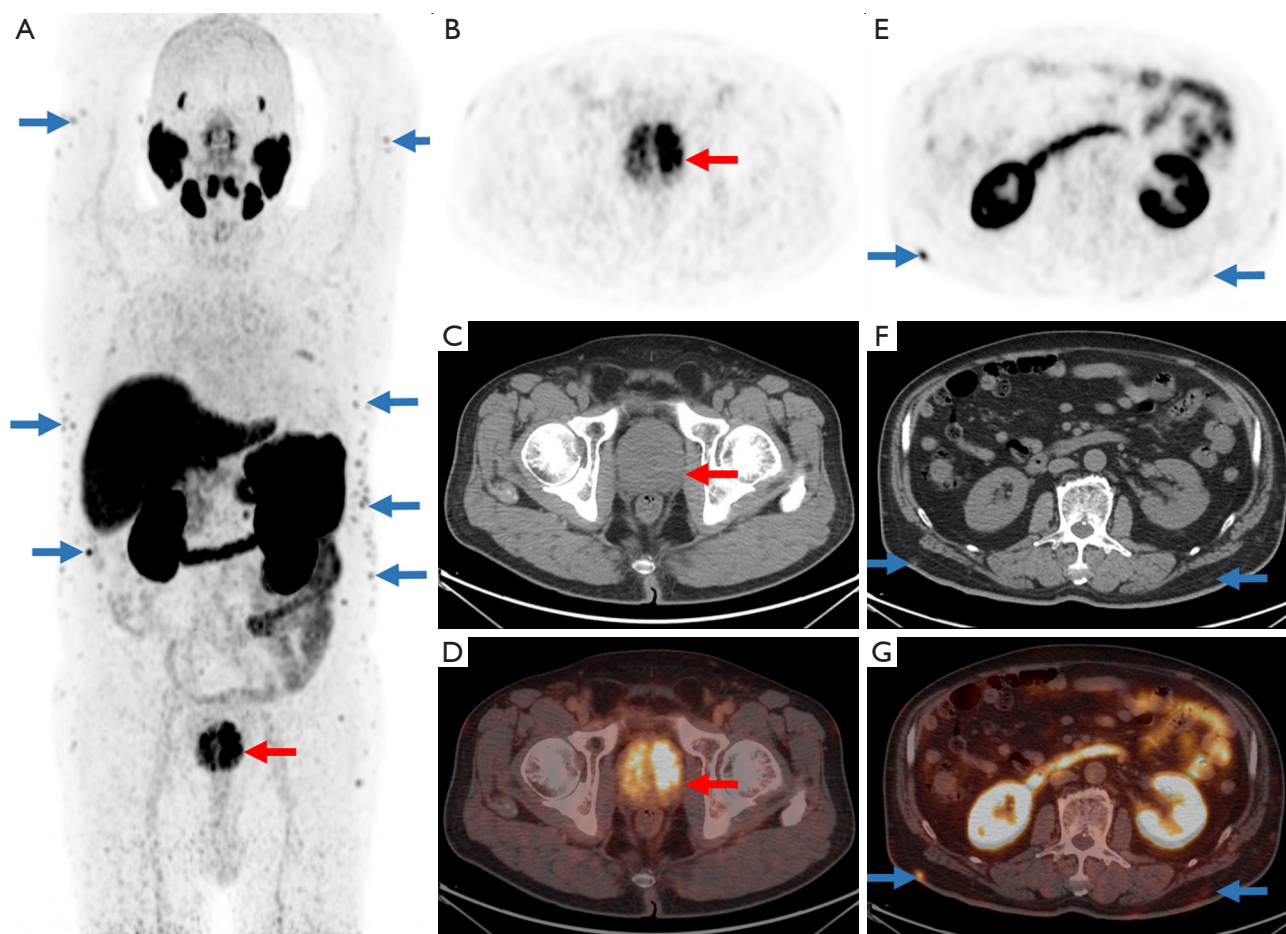
After incision, the nodules had an obvious envelope and were lobulated. The cut surface was yellow, and the edges were dark red due to blood vessel components. Microscopically, in addition to mature lobulated adipose in the tissues, there were still proliferating capillaries that grew from the capsule along the septal connective tissue to

the center. Endothelial cells proliferated and the lumen was narrow. Some could only accommodate 1 to 2 red blood cells or were completely occluded (*Figure 2B*). The collagen fibers in the interstitium were homogeneous, lightly stained red with eosin, and had no signs of inflammation or malignancy such as increased cell proliferation, nuclear polymorphisms, or mitotic activity. These features were consistent with angioliopoma (11). PSMA immunoreactivity results are shown in *Figure 2*, which demonstrated strong positive cytoplasmic PSMA staining in lesional prostate cancer cells in the prostate carcinoma and mild-to-moderate positive cytoplasmic capillary PSMA staining in the angioliopoma lesion. Mature adipocytes did not express PSMA (*Figure 2D*). Based on the <sup>18</sup>F-PSMA PET/CT imaging, operative, and histological findings, the final diagnosis was prostate cancer with multiple subcutaneous angioliopomas. PSMA-based PET/CT uptake in angioliopomas was caused by PSMA expression in capillaries or the vasculature. The timeline of the case is depicted in *Figure 3*.

Study protocols accorded with recommendations of the Commission of Medical Research Involving Human Subjects at Region of Xiangya Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

### Discussion

PSMA is a type II transmembrane glycoprotein, which consists of 19 intracellular amino acids, 24 transmembrane amino acids, and 707 extracellular amino acids. It is physiologically expressed in epithelial cells around the top of the prostate duct, and in some other tissues in the cytoplasm (e.g., renal cortex, duodenum, ileum, salivary glands, lacrimal glands, and coeliac ganglia). Functionally, it has both folate hydrolase activity and N-acetylated  $\alpha$ -linked acidic dipeptidase (NAALADase) activity (1,4). In dysplastic or cancerous tissues, PSMA can metastasize from the apical membrane to the lumen surface of the catheter, and the tumor tissues that transform to androgen-independent prostate cancer have a higher expression of PSMA. In addition, PSMA is also expressed in other tumor tissues or neovascular tissues other than prostate cancer, including lung cancers, colonic adenocarcinomas, clear cell renal carcinomas, transitional cell carcinomas, schwannomas, malignant melanomas, and osteosarcomas (12). The



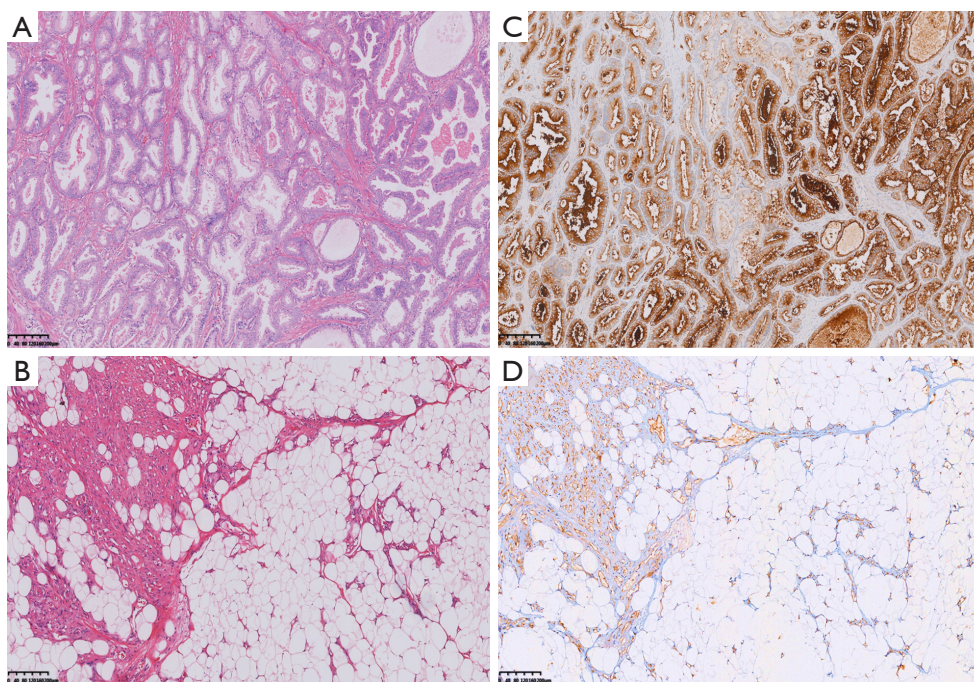
**Figure 1**  $^{18}\text{F}$ -PSMA-1007 PET/CT images of the patient presenting with PSMA-positive lesions. The maximum intensity projection image (MIP) and PET/CT axial images showed intense focal PSMA uptake in the zone of the prostate gland (red arrows). Additionally, the PET/CT scan demonstrated multiple PSMA-avid subcutaneous fatty density nodules. The highest level of uptake occurred in the nodules of the right lower back, with a SUVmax value of 8.2 (blue arrows) (A, PET MIP; B and E, PET; C and F, CT; D and G, fusion). PET/CT, positron emission tomography/computed tomography; PSMA, prostate specific membrane antigen; SUV, standardized uptake value.

histopathological expression of PSMA in these malignancies is usually confined to the neovasculature rather than to the tumor cells. PSMA uptake intensity is also weaker, and the patterns of distribution are very different from those of prostate cancer. Possible pathophysiological mechanisms include the increase in local folic acid concentration in the tissue from the folate hydrolase activity of PSMA (1,13). Folic acid increases the level of nitric oxide by promoting the synthesis of endothelial nitric oxide synthase, which ultimately facilitates angiogenesis (14). Tumor-associated neovascularization is further related to high aggressiveness, high metastasis ability, and unfavorable prognosis (15). In general, high neovascular PSMA expression is more common in malignant tumors than in moderate or benign

tumors (4).

Angiolipoma is a special type of lipoma that is formed by a mixture of mature adipocytes and abnormally proliferating angiomas. It is generally seen in young men, and is a benign tumor that grows very slowly (16). The presence of fibrinous hyaline thrombi in the vascular cavity is an important feature for the diagnosis of angiolipoma (11). Angiolipoma in an older patient is a very rare phenomenon, and only 2 cases, as diagnosed by PET/CT, have been previously reported. In one case, the patient had a focal angiolipoma with increased  $^{18}\text{F}$ -FDG PET uptake in the left lower abdominal wall. The authors thought this might have been due to hypervascularity, blood stasis, and congestion in the vascular structure, which accelerates inflammatory processes



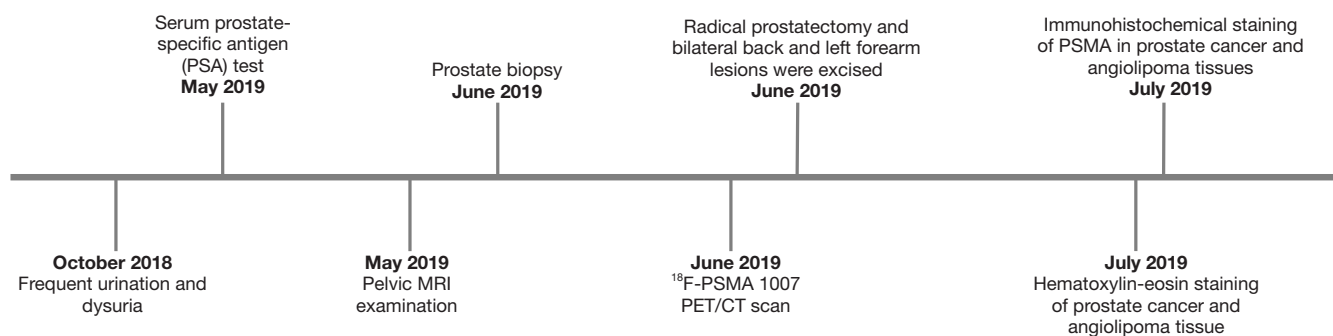


**Figure 2** Hematoxylin and eosin (HE) and PSMA staining in prostate carcinoma and angioliopoma. (A,B) Histopathological examinations revealed prostate carcinoma and angioliopoma; (B) microscopic examinations of the angioliopoma showed a mixture of mature adipose tissue with hyperactive vascular tissue; (C) PSMA staining was strongly positive in prostate cancer tissue; (D) angioliopoma nodular tissue, on viable adipocytic cells, showing mild-to-moderate staining of PSMA in the capillaries. HE, hematoxylin and eosin; PSMA, prostate specific membrane antigen.

and leads to high  $^{18}\text{F}$ -FDG uptake (9). Another case report found high uptake of  $^{68}\text{Ga}$ -PSMA in subcutaneous angioliopoma, but did not provide further in-depth analysis of the potential causes (8). Our case report demonstrated that  $^{18}\text{F}$ -PSMA-1007 PET uptake in angioliopoma is associated with PSMA expression levels in the capillaries or vasculature. The cause of high uptake of PSMA in benign lesions has not been thoroughly investigated in previous studies. Hofvander *et al.* found low-level protein kinase D2 (PRKD2) gene mutations in angioliopomas (17). PRKD2 is a main component of a regulatory loop that tightly modulates  $\beta$ 1 integrins and PSMA. Active PSMA facilitates integrin signal transduction, endothelial nitric oxide synthase regeneration, and p21-activated kinase (PAK) activation, leading to increased invasion and adhesion of endothelial cells, angiogenesis, and distorted capillary networks within the angioliopomas (18,19).

PSMA, also known as glutamate carboxypeptidase II, has been shown to not only be highly expressed in prostate cancer, but also in various non-prostatic tissues, including the brain and other benign processes. Understanding the

physiological distribution of PSMA and other causes for uptake is therefore necessary to minimize false-positive imaging findings. Recently,  $^{18}\text{F}$ -labeled PSMA has been shown to be a promising labelling strategy and potential clinical alternative for  $^{68}\text{Ga}$ -labeled counterparts. There are some major principle advantages of radiofluorinated tracers over  $^{68}\text{Ga}$ -labeled PSMA ligands, such as a longer half-life (110 *vs.* 68 min), centralized production and distribution leading to cost savings, the possibility of large-batch production (cyclotron-produced  $^{18}\text{F}$  *vs.* generator-produced  $^{68}\text{Ga}$ ), and the lower positron energy of  $^{18}\text{F}$  compared to  $^{68}\text{Ga}$ , potentially improving spatial resolution and reducing blurring effects. However, studies on biochemical recurrence after radical prostatectomy have shown that the number of benign lesions with increased PSMA-ligand uptake and the number of recurrent lesions were both considerably higher for  $^{18}\text{F}$ -PSMA PET/CT than for  $^{68}\text{Ga}$ -PSMA PET/CT (20,21). This needs to be verified by further studies with larger sample sizes, and also indicates that we need more sophisticated reader training to avoid pitfalls and reduce false-positive rates as much as possible.



**Figure 3** Image depicting the timeline of this case.

Many questions remain to be answered, among which include the method for confirming the final pathological results of lesions in which the uptake of two isotope-labeled PSMA ligands are inconsistent and cannot be biopsied. This case report had some limitations. Multiple subcutaneous angiolipomas are a rare type of benign tumor, and so the high uptake or expression of capillary PSMA in this case of angiolipoma can only provide an interpretation in the context of benign tumors with a high expression of PSMA. More benign lesions with a high uptake of PSMA and possible causes need to be further investigated in order to minimize false-positive imaging findings.

## Conclusions

In summary, apart from the known high uptake of PSMA in prostate carcinoma, our study demonstrated that <sup>18</sup>F-PSMA-1007 PET/CT uptake in multiple angiolipomas can be caused by PSMA expression in capillaries. Further knowledge regarding the causes of PSMA uptake is essential for minimizing false-positive imaging isotope-labeled PSMA PET findings.

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## Footnote

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Study protocols accorded with recommendations of the Commission of Medical Research Involving Human Subjects at Region of Xiangya Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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