Two cases of positive ^{68}Ga-PSMA-11 PET imaging in stroke

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Abstract
Gallium-68-prostate-specific membrane antigen (^{68}Ga-PSMA-11) positron emission tomography/computed tomography (PET/CT) is a key imaging modality for evaluating prostate cancer. Here we report two cases of unexpected positive ^{68}Ga-PSMA-11 uptake in stroke lesions during prostate cancer assessment. The first patient suffered from cerebral hemorrhage in the right frontal lobe, and the second patient was diagnosed with acute cerebral infarction in the right occipital lobe. The abnormal PSMA uptake in both lesions was attributed to pathological angiogenesis and activated endothelial cells in the process of tissue repair after stroke. Since stroke may mimic brain metastasis on ^{68}Ga-PSMA-11 PET/CT, radiologists and nuclear medicine physicians need to integrate clinical manifestations and multimodal imaging results for accurate diagnosis, so as to prevent diagnostic errors in clinical practice.

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Introduction

Prostate-specific membrane antigen (PSMA) imaging is a nuclear medicine-based functional imaging modality that utilizes the high expression of PSMA in specific cell types. Though traditionally recognized as a biomarker for prostate cancer, accumulating evidence indicates that PSMA is also expressed in the endothelial cells of neovasculature associated with various solid tumors [1]. In response to active bleeding or acute ischemia, the body initiates rapid neovascularization to facilitate tissue repair, during which endothelial cells in newly formed vessels exhibit marked upregulation of PSMA. We present two cases of stroke-one case of cerebral hemorrhage and the other case of cerebral infarction-detected via PSMA positron emission tomography (PET) imaging. Following intravenous administration of a radiolabeled gallium-68 (^{68}Ga)-PSMA-11 inhibitor, selective binding occurs between the tracer and PSMA-expressing endothelial cells. Subsequent PSMA positron emission tomography (PET) imaging enables precise localization of bleeding foci and infarct location associated with pathological neovascularization. Compared to conventional methods for bleeding and infarct localization, this technique demonstrates superior target-to-background contrast and spatial resolution. It holds considerable promise for the detection of intermittent, low-volume, or occult gastrointestinal bleeding, or subacute cerebral infarction, suggesting significant potential for future clinical applications.

Case Report

Case 1

A 72-year-old male was found to have a baseline prostate-specific antigen (PSA) level exceeding 100ng/mL during a physical examination three months prior. A biopsy conducted at a local hospital confirmed the diagnosis of prostate cancer with a Gleason score of 8. The patient subsequently underwent androgen deprivation therapy (ADT) in combination with bicalutamide for three months at a local hospital. Post-treatment laboratory evaluations revealed a decline in total PSA to 3.157ng/mL. He was then scheduled for ^{68}Ga-PSMA-11 PET/computed tomography (CT) imaging to evaluate treatment response and determine his eligibility for potential surgical intervention. One week earlier, multi-sequence brain magnetic resonance imaging (MRI) revealed a hemor-

rhagic lesion located in the right frontal lobe (Figure 1). Prostate-specific membrane antigen PET imaging demonstrated elevated PSMA expression following treatment for prostate cancer, indicating residual tumor activity. Whole-body imaging did not reveal any metastatic lesions, and a ring-shaped focus with mildly increased PSMA uptake was identified in the right frontal lobe, raising suspicion for a metastatic tumor (Figure 2). However, the findings of brain MRI and PSMA PET/ CT were discordant with each other. Following a multidisciplinary consultation, it was recommended to perform susceptibility-weighted imaging (SWI) of the brain. After integration with the findings from the initial MRI examination, the right frontal lobe lesion was identified as cerebral hemorrhage rather than brain metastasis. The patient is thus deemed eligible for subsequent surgical treatment of prostate cancer. Both MRI scans confirmed the presence of cerebral hemorrhage.

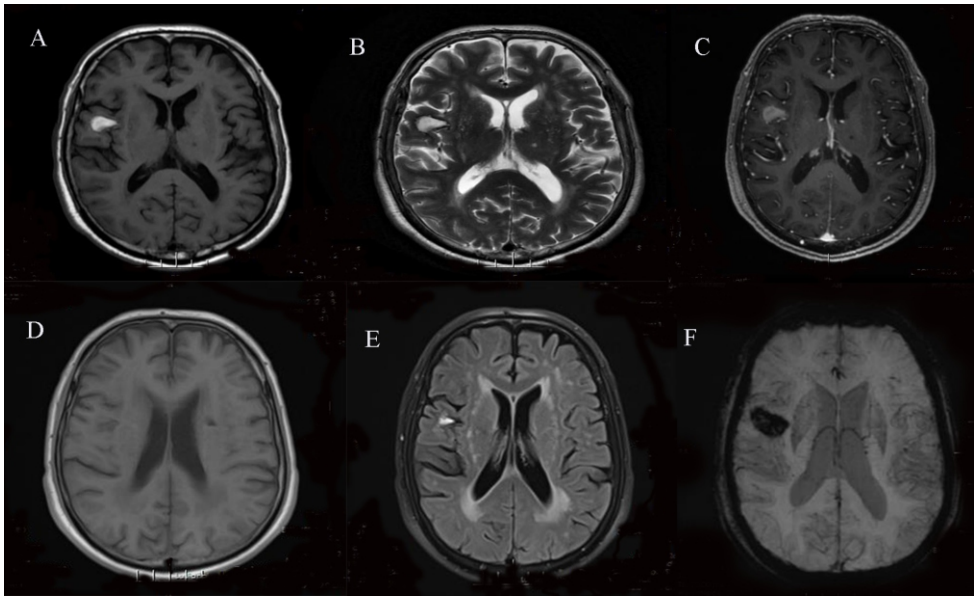

Figure 1. Axial T1-weighted, T2-weighted and T1-enhanced sequences (A-C) of brain MRI images indicate a lesion in the right frontal lobe exhibiting hyperintensity without contrast enhancement, consistent with cerebral hemorrhage. Twelve days later, a follow-up brain MRI examination was performed. Axial T1-weighted imaging (D) revealed a reduction in lesion volume with a corresponding decrease in signal intensity to hypointensity. Axial fluid-attenuated inversion recovery (FLAIR) imaging (E) demonstrated a hyperintense signal, while SWI (F) displayed a hypointense signal. These features are indicative of post-hemorrhagic changes and correlate with partial resorption of the hematoma.

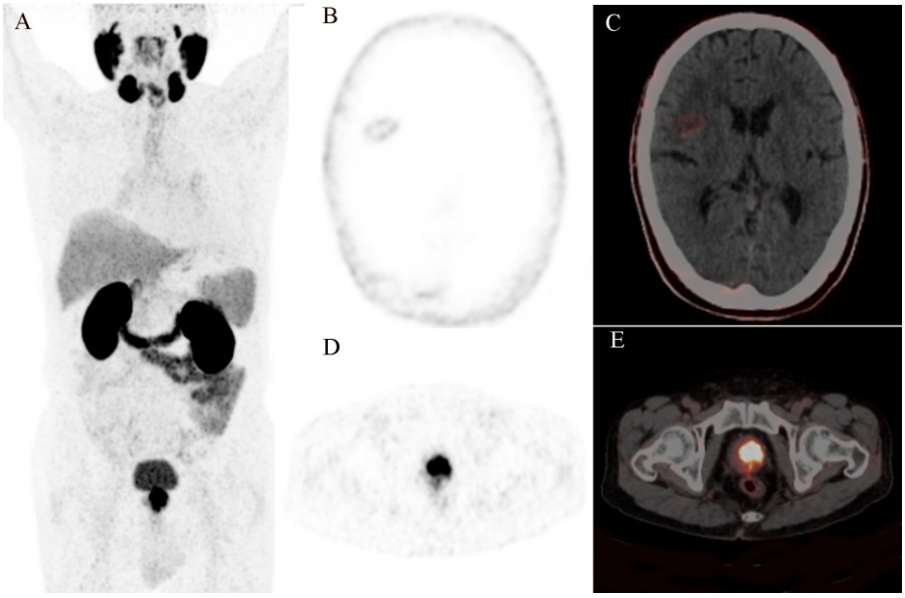

Figure 2. Maximum intensity projection (MIP) image (A) revealed abnormal increased PSMA imaging agent in the prostate area, along with physiological uptake or excretion in the bilateral lacrimal glands, parotid glands, submandibular glands, bilateral kidneys, part of the small intestine, and the bladder. Axial PET and fused image (B-C) demonstrated mild ring-shaped PSMA imaging agent uptake in the frontal lobe, with a maximum standardized uptake value (SUVmax) of 0.8 (B), accompanied by a heterogeneous hypodensity lesion (C). Additional axial PET and fused images (D-E) showed nodular abnormal increased uptake of the PSMA agent within the prostate, suggestive of high PSMA expression, with a SUVmax of 15.2. These findings are consistent with the imaging features of prostate cancer.

Case 2

An 83-year-old male with a history of prostate cancer underwent combined chemotherapy and radiotherapy over a 9-year period, with ongoing maintenance therapy involving oral rivaroxaban. Recently, his total PSA level showed a slight elevation to 0.841ng/mL (reference range: 0-4ng/mL). Twelve days prior to this report, he was admitted to the hospital due to left-sided limb weakness. On admission, brain MRI revealed an acute infarction in the right occipital lobe (Figure 3). To evaluate his systemic condition following prostate cancer treatment, a comprehensive ^{68}Ga-PSMA-11 PET imaging examination was performed, revealing a localized area of increased ^{68}Ga-PSMA-11 uptake in the right occipital lobe and the left lateral lamina of the third lumbar vertebra (Figure 4).

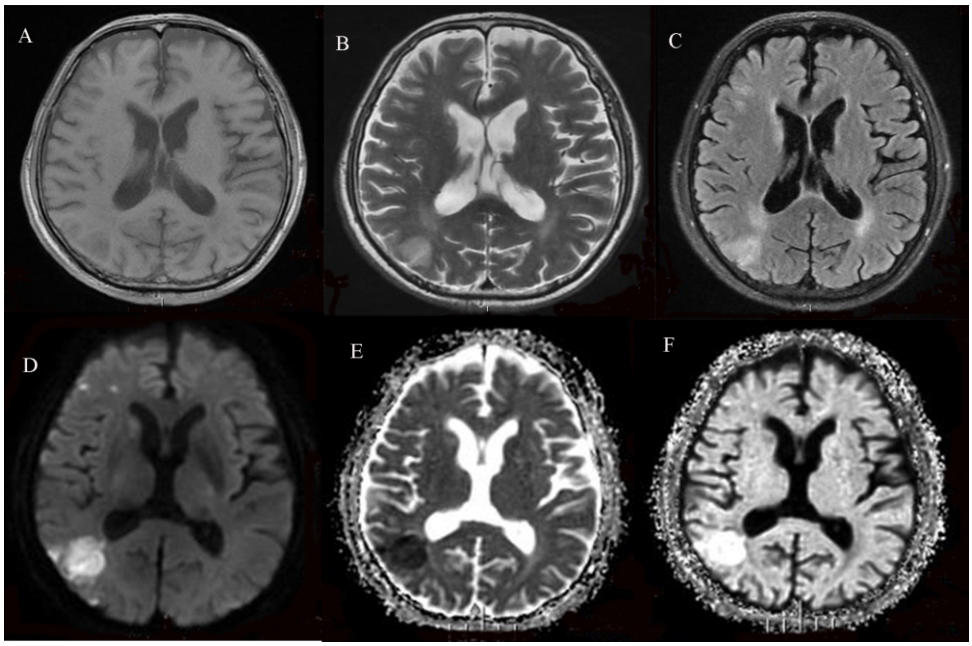

Figure 3. A patchy slightly hypointense and hyperintense signal in the right occipital lobe was seen on axial T1-weighted and T2-weighted images (A, B). The T2WI-FLAIR sequence demonstrates a mildly high signal intensity in the right occipital lobe (C). The lesion located in the right occipital lobe showed hyperintense signal intensity on diffusion-weighted imaging (DWI), hypointense signal intensity on apparent diffusion coefficient (ADC), and hyperintense signal intensity on exponential ADC (eADC), suggesting restricted diffusion (D-F).

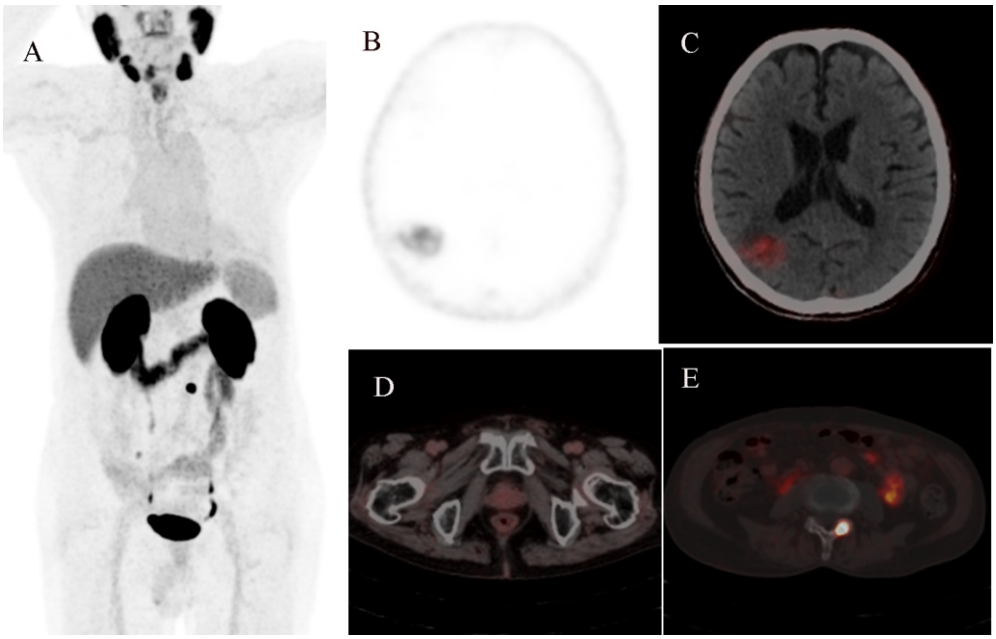

Figure 4. The PET MIP image demonstrates physiological uptake in the bilateral parotid glands, submandibular glands, kidneys, and portions of the intestinal tract. A focal nodular lesion with increased uptake of the imaging agent is observed in the central lower abdomen (A). Axial PET and fused PET/CT images reveal patchy increased PSMA radiotracer uptake in the right occipital lobe, with a maximum SUV of 2.7 (B-C). No PSMA increase was seen after prostate cancer treatment on axial fusion PET/CT imaging (D). Focal PSMA uptake was observed in the left pedicle plate of the L3 vertebra, suggesting a metastatic tumor (E).

Discussion

Prostate-specific membrane antigen is a type II transmembrane glycoprotein with low expression in normal prostate epithelial cells but is highly expressed on the surface of prostate cancer cells [2]. Its expression in prostate cancer is characterized by high specificity and heterogeneity. In clinical practice, radiolabeled PSMA ligands (either fluorine-18 (^{18}F) or gallium-68 (^{68}Ga)-labeled) are employed for molecular imaging, enabling highly specific binding through recognition of the extracellular domain of PSMA. This approach is widely used for the imaging, diagnosis, staging, and post-treatment evaluation of prostate cancer. However, in clinical observations, certain non-neoplastic hemorrhagic apoplexy or ischemic stroke cases have also demonstrated positive PSMA uptake. Under physiological conditions, PSMA is either undetectable or expressed at very low levels in the endothelial cells of cerebral vessels. Nevertheless, during pathological angiogenesis or vascular repair processes, PSMA is markedly upregulated in newly formed and activated vascular endothelial cells. The mechanism underlying PSMA PET imaging in cerebral hemorrhage or ischemia does not involve the presence of prostate cancer cells; rather, it results from tissue repair and inflammatory responses triggered by hemorrhage or ischemia, which induce neovascularization around the lesion. Some newly formed vascular endothelial cells demonstrate low to moderate PSMA uptake, which is associated with the molecular function of PSMA and the local microenvironmental conditions, allowing them to be selectively targeted and visualized by the radiotracer [3].

The first case underwent ^{68}Ga-PSMA PET/CT imaging prior to scheduled prostate cancer surgery. Incidentally, a mild PSMA-avid lesion was identified in the right frontal lobe. Subsequent MRI follow-up suggested that this finding represented a hemorrhagic stroke. However, the underlying etiology of the hemorrhage remains unclear. Potential etiologies hypothesized include hypertension-induced vascular rupture and small vascular malformations. During the absorption phase of cerebral hemorrhage, proliferating astrocytes predominantly form glial scars to fill and isolate the affected region. These scars also contain newly formed blood vessels and a limited number of residual macrophages. The second case was ischemic stroke, in which inflammation-mediated angiogenesis plays a crucial role in restoring blood supply, delivering nutrients and oxygen, and supporting neuronal survival and regeneration [4]. PSMA imaging agents can be nonspecifically taken up by the endothelial cells of newly formed blood vessels, which constitutes the underlying mechanism of PSMA imaging for hematoma detection. There are relatively few literature reports regarding PSMA PET/CT imaging of cerebral hemorrhage [5, 6]. Most of these cases are predominantly identified incidentally during PSMA PET/CT imaging examinations conducted for prostate cancer and often lack neurological symptoms associated with cerebral hemorrhage. This absence of specific clinical manifestations may lead to misinterpretation as metastatic lesions. Therefore, increased attention and careful evaluation are warranted in nuclear medicine diagnostics. Notably, cerebral hemorrhage or ischemic stroke may manifest as false-positive findings on PSMA PET/CT imaging, which can be mistaken for metastatic lesions in patients with both prostate cancer and cerebral apoplexy. Nuclear medicine physicians are advised to conduct a comprehensive analysis of the patient's clinical and imaging data to ensure an accurate diagnosis and prevent diagnostic errors.

In conclusion, both cerebral hemorrhage and ischemic stroke can present as positive PSMA PET findings due to neovascularization-related PSMA upregulation. Awareness of this phenomenon is essential to avoid misdiagnosis as metastatic disease in patients undergoing ^{68}Ga-PSMA-11 PET/CT imaging for prostate cancer.

The authors declare that they have no conflicts of interest.

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