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PSMA-positive Secondary Tumors in ^{68}Ga-PSMA PET/CT Imaging in Patients with Prostate Cancer

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Abstract

Objective: The objective of this research was to examine the prostate-specific membrane antigen (PSMA)-positive secondary tumor incidence in ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) imaging in patients with prostate cancer (PCa).

Methods: Data from 605 ^{68}Ga-PSMA PET/CT images of 506 PCa patients used for staging or restaging were analyzed retrospectively. Further, documented separately, PSMA-positive lesions were found not to be PCa-related and were then suspected as secondary tumors. The results were analyzed from those lesions that were histopathologically verified.

Results: Nine patients (1.8%) had a PSMA-positive lesion that was believed to be a secondary tumor. Of these lesions, five (1%) were histopathologically confirmed, and secondary tumors were diagnosed (namely, squamous cell non-small cell lung cancer, papillary thyroid cancer (TCa) lymph node metastasis, minimally invasive TCa, colon cancer and liver metastases, and fibrohistiocytic tumor). The mean serum PSA value for patients diagnosed with secondary tumor was 29.42 (0.01-142.22) ng/mL. For PSMA-positive secondary tumor lesions, the mean maximum standard unit value was 9.74 (3.9-15).

Conclusion: Especially in the presence of atypical location and insufficient serum PSA values, PSMA-positive lesions should be considered secondary tumors, and differential diagnostic studies should be conducted.

Keywords: ^{68}Ga-PSMA PET/CT, PSMA uptake, secondary tumor

INTRODUCTION

Prostate-specific membrane antigen (PSMA), also referred to as folate hydrolase I or glutamate carboxypeptidase II, is expressed at elevated levels in prostatic adenocarcinoma prostate cancer (PCa) cells 100-1000 times that of normal prostate tissue (1,2). Moreover, PSMA expression may increase with high tumor grade/stage and also with tumor dedifferentiation, metastatic disease, and hormone resistance (1,2). This is the target site for ^{68}Ga-labeled agents that bind and cause the agent to be internalized, thereby allowing detection on positron emission tomography (PET) imaging. Compared to traditional imaging, ^{68}Ga-PSMA PET/computed tomography (CT) has superior diagnostic capabilities to detect tumoral focus in primary staging and biochemical recurrence (BCR) of patients with PCa (3-5).

^{68}Ga-PSMA uptake can usually be seen in the salivary glands, nasopharynx, vocal cords, thyroid gland, duodenum, small intestines, spleen, liver, pancreas, stomach, adrenal gland, kidneys, rectum, testes, and varying degrees of vertebral bone marrow (6,7). In addition, PSMA expression was demonstrated in a number of nonprostatic malignant and non-malignant conditions found in ^{68}Ga-PSMA PET/CT (8-10) and was also seen in neovascular capillary endothelium in the peritumoral areas of a variety of epithelial malignancies (2). This condition resulted in the discovery of incidental non-prostatic tumors on ^{68}Ga-PSMA PET/CT imaging performed for both primary staging and BCR and led to its use for diagnostic purposes for malignancies such as hepatocellular Ca and renal Ca. In this study, the incidence of PSMA-positive secondary tumors found in ^{68}Ga-PSMA PET/CT

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imaging were examined and histopathologic findings of these tumors were evaluated.

METHODS

Patients

Retrospectively, the medical history and imaging data of PCa patients who underwent ^{68}Ga-PSMA-PET/CT at our nuclear medicine department from July 2017 to December 2019 were analyzed. The PSMA-positive lesions believed to be secondary tumors of these patients were examined for imaging and histopathologic findings. Patients with secondary malignancy prior to ^{68}Ga-PSMA-PET/CT imaging were excluded from the study. If lesions were found, localization, CT findings, and clinical findings were evaluated together, and pathologies with no association with PCa and high likelihood of being benign were not included.

All patients signed written informed consent forms for the purpose of reviewing and publishing their results. Hence, this study was accepted by the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (01.07.2020/14).

Imaging and Analysis

Patients were imaged using an integrated PET/CT scanner consisting of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). Each patient was given a standardized weight-based dose of 2 MBq/kg (range 70-180 MBq) ^{68}Ga-PSMA. Further, PET/CT scan was performed at 60 min post-injection with an emission time of 3 min per bed position from the vertex to the upper thigh. Prior to emission imaging, low-dose CT for attenuation correction and anatomic localization was performed with the following parameters: 50 mA, 140 kV, and 5 mm section thickness. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany). The images were then interpreted by an experienced nuclear medicine physician on the basis of a visual examination with knowledge of the patient's clinical history and the findings of previous imaging studies. A positive scan was characterized as such when the PSMA uptake was visually above the background and did not correspond to the physiologic distribution sites. The maximum standardized uptake values (SUV_{max}) of each lesion were determined by the region of interest applied in the transaxial attenuation-corrected PET slice with the highest uptake.

Patients were suspected of developing PSMA-positive secondary tumor in the presence of one of the following criteria:

- A lesion with increased PSMA uptake was detected at a site that was unexpected on the basis of the PCa metastasis pattern.

- Inconsistency between PSMA-positive lesion, patient clinical progression, and serum PSA values was found.

Any site of incidental PSMA uptake found not to be PCa-related and suspected of being a secondary tumor was documented separately. PSMA-positive lesions suspected of secondary tumors were verified by histopathologic evaluation whenever possible.

Statistical Analysis

During the evaluation of the study data, descriptive statistical methods such as mean, median, frequency, ratio, minimum, and maximum value were used.

RESULTS

Retrospectively, data from 605 ^{68}Ga-PSMA PET/CT images performed for staging or restaging of 506 PCa patients were reevaluated. Nine (1.8%) of these patients were reported as having PSMA-positive lesion suspected of being a secondary tumor. The mean age of patients was 67.4 years (52-79) with six patients having ^{68}Ga-PSMA PET/CT imaging for restaging and three patients having it for staging purposes. Of these lesions, five (1%) were histopathologically confirmed and had the following secondary tumor diagnoses (Table 1): squamous cell non-small cell lung cancer (NSCLC) presenting as mass lesion in the left lung (Figure 1), papillary thyroid cancer (TCa) presenting as lymph node in the right cervical region, minimally invasive TCa as a nodular lesion in the right lobe of the thyroid, metastatic colon cancer presenting as multiple hypodense lesions in the liver and lesion in the descending colon, and fibrohistiocytic tumor presenting as subcutaneous

Table 1. General characteristics of histopathologically verified PSMA-positive secondary tumor

PSMA-positive lesion	PSA	SUV_{max}	Histopathological diagnosis
Mass lesion at left lung	4.65	7.84	Squamous cell lung cancer
Nodular lesion at right thyroid lobe	0.01	15	Minimally invasive thyroid cancer
Lymph node at right cervical chain	0.01	8.09	Papillary thyroid cancer lymph node metastasis
Descending colon lesion to multiple liver lesion	142.2	13.86	Colon cancer to liver metastases
Subcutaneous lesion at dorsal region	0.2	3.9	Fibrohistiocytic tumor

PSMA: Prostate-specific membrane antigen, PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake values

lesion in the dorsal region. Of these patients, the mean serum PSA value was 29.42 (0.01-142.22) ng/mL. Cases with PSMA-positive secondary tumor diagnosis had a mean SUV_{max} value of 9.74 (3.9-15). In the case with histopathologic diagnosis of fibrohistiocytic tumor, the SUV_{max} lesion value was lower than the physiologic SUV_{max} values for the liver and higher than the other cases. With histopathologic investigation, three patients with a diagnosis of malignancy were treated, while two cases with biopsy were included in the treatment program for medical oncology. In three patients with increased PSMA expression in the thyroid gland (SUV_{max} values 3.54, 5.55, and 2.27), no advanced research could be conducted due to the clinical condition of the patients or follow-up in an outpatient center. A patient with PSMA-positive lesion (SUV_{max} 25.13) in the spleen parenchyma had a diagnosis of hemangioma with magnetic resonance imaging.

DISCUSSION

While prostate-specific, PSMA is not specific for PCa. PSMA-positive incidental secondary tumor lesions have been observed since the first application of ^{68}Ga-PSMA PET/CT imaging to PCa patients. PSMA is expressed in various forms of tumor neovasculature, such as renal cell carcinomas, bladder carcinomas, colonic adenocarcinomas, gastric cancers, TCa, gliomas, LC, malignant melanomas, osteosarcomas, and soft tissue tumors, but not normal tissue vasculature (11-17). There are several publications in the literature on incidental secondary malignancies found on ^{68}Ga-PSMA PET/CT imaging performed for the purpose of staging or restaging patients with PCa (18,19). Hepatocellular carcinoma, renal adenocarcinoma, follicular and papillary TCa, follicular lymphoma, multiple myeloma, gastrointestinal stromal tumor, rectal adenocarcinoma, colon adenocarcinoma, penile squamous cell carcinoma (SCC), primary LC, breast cancer, urothelial cancer, and oropharynx SCC (20-33) were included in these articles.

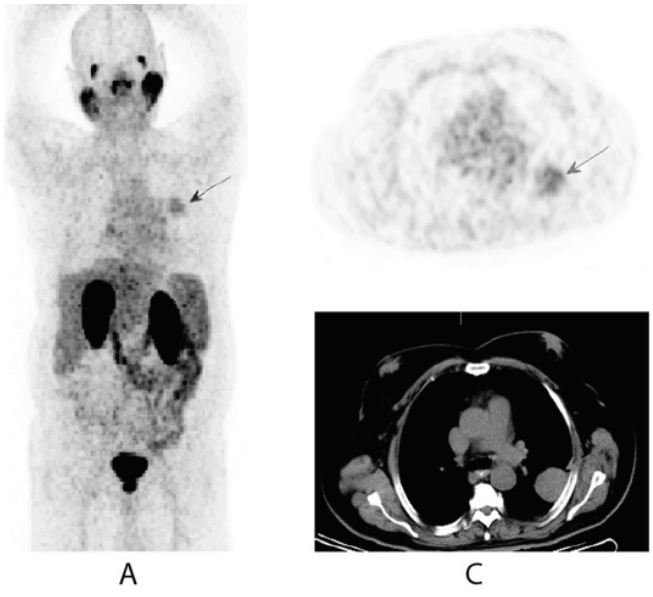

Figure 1. A 73-year-old PCa patient is imaged with ^{68}Ga PSMA PET/CT for restaging. The serum PSA value was 4.65 ng/mL. PSMA expressing lung mass was found in the left lung (SUV_{max}: 7.84) on ^{68}Ga PSMA PET/CT imaging (arrow). Histopathological evaluation revealed squamous cell NSCLC

PCa: Prostate cancer, PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake values, NSCLC: Non-small cell lung cancer

In this 506-patient cohort group, 1.8% of patients were reported as having PSMA-positive incidental lesions which were suspected as a secondary tumor. Of these lesions, five (1%) were histopathologically verified, and secondary tumor diagnosis was made (papillary TCa, minimally invasive TCa, NSCLC, colon cancer, and fibrohistiocytic tumor). Osman et al. (34) observed synchronous primary malignancy in 5 patients in a 764 PCa case series of PET/CT imaging performed (0.7%, 2 lung adenocarcinoma, 1 diffuse B-cell lymphoma, 1 PCa, and 1 SCC of the base of the tongue).

In this study, TCa was the most frequently identified secondary incidental tumor. A diagnosis of metastatic papillary TCa was made in one patient with histopathologic examination of lymph nodes in the cervical region. This patient had a papillary TCa focus of 0.5 cm identified with thyroidectomy pathology. Pathologic involvement of the thyroid gland was not present on ^{68}Ga-PSMA PET/CT imaging. It was concluded that the small size of the primary lesion was effective due to the lack of detection of PSMA-positive lesion in the thyroid gland. One patient had minimally invasive follicular TCa diagnostic sites with thyroidectomy pathology of PSMA-positive thyroid lesion. Immunohistochemistry studies of TCa cases showed that neovascular PSMA expression was more common in TCa relative to benign thyroid pathologies and that there were high levels of PSMA expression in poorly or undifferentiated and aggressive TCa (13,34). This property resulted in the use of ^{68}Ga-PSMA PET/CT imaging and potential radionuclide treatment for metastasis identification in high thyroglobulin and radioiodine-negative TCa, in particular (35).

One of our cases diagnosed with an incidental PSMA-positive secondary tumor had squamous cell NSCLC. In the literature, both squamous and adenocarcinoma NSCLC cases have been reported to be identified with ^{68}Ga-PSMA PET/CT imaging (28,36,37). Schmidt et al. (11) immunohistochemistry studies on NSLC cases found neovascular PSMA expression in 49% of NSCLC

and tumor cell PSMA expression in 6%. High neovascular PSMA expression was also reported to be associated with higher tumor grading.

In this study, a patient with PSMA-positive colon cancer in the descending colon also demonstrated PSMA expression in liver metastases. Cases of PSMA-positive colorectal cancer have been documented in the literature, and immunohistochemistry studies have reported that higher-grade colorectal tumors appear to have higher PSMA expression and higher risk of distant metastases and vascular invasion. However, there was no statistical difference in overall survival or disease-free survival based on PSMA expression (16,27,28).

In analysis, the mean serum PSA value for five patients with histopathologic verification of secondary tumor diagnosis was 29.42 (0.01-142.22) ng/mL. There were two patients with 0.01 ng/mL and one patient with 0.2 ng/mL, whereas three patients had low serum PSA value with PSMA-positive lesion identified. When lesions are evaluated with anatomic localization, the low serum PSA value should be assessed as a factor warning of the presence of pathology outside the prostate.

Study Limitations

The most significant limitation of this retrospectively designed study is that all incidental PSMA-positive lesions found on ^{68}Ga PSMA PET/CT imaging were not histopathologically verified. Another drawback is that differential diagnosis of synchronous secondary malignancies could not be made because advanced diagnostic studies could not be conducted in patients with extensive visceral metastases due to the clinical status and ethical reasons.

CONCLUSION

PCa patients may rarely have PSMA-positive secondary tumors found in ^{68}Ga PSMA PET/CT images. In particular, considering the CT properties of the atypical PCa metastasis location and the presence of PSMA-positive lesions that do not respond to patient clinical symptoms, consideration should be given to the possibility of secondary tumors and differential diagnostic studies be performed.

Ethics

Ethics Committee Approval: Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (01.07.2020/14).

Informed Consent: All patients signed written informed consent forms for the purpose of reviewing and publishing their results.

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