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Original Article

Lung uptake detected by ^{68}Ga-PSMA-11 PET/CT in prostate cancer patients with SARS-CoV-2: a case series

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Abstract: Coronavirus disease 2019 (COVID-19) pathology is associated with neoangiogenesis and interstitial pneumonia. ^{68}Ga-PSMA-11-PET/CT is able to image in vivo PSMA (Prostate-Specific Membrane Antigen) expression on both prostate cancer (PCa) cells and neovasculature endothelial cells. The aim of the case series was to explore pulmonary PSMA expression not related to cancer in patients with PCa and concomitant COVID-19. In this retrospective, multicenter case series, patients who underwent ^{68}Ga-PSMA-11-PET/CT for PCa and concomitant proven COVID-19 infection were analyzed. Patients were stratified according to ^{68}Ga-PSMA-11 intensity of uptake in the lung (SUVmax). Low uptake: < blood pool; mild-to-moderate uptake: > blood pool and < liver; intense uptake: > liver. Potential correlation between pulmonary ^{68}Ga-PSMA-11 uptake not related to PCa and CT patterns typical for COVID-19 was assessed. Nine patients were included, all of them presenting abnormal ^{68}Ga-PSMA-11 uptake, at different grades: 2/9 low, 6/9 mild-to-moderate, 1/9 high. Uptake distribution was generally bilateral, peripheral and posterior, positively matching with ground-glass CT alterations in 7/9 (78%) patients, while mismatch was observed in 2/9 (22%). 1/9 patients presented PCa lung metastases at ^{68}Ga-PSMA-11. ^{68}Ga-PSMA-11-PET/CT detected increased PSMA uptake within the lung, not related to PCa, matching with CT typical COVID-19 patterns in almost all patients. Further studies are needed to evaluate the role of ^{68}Ga-PSMA-11 PET in COVID-19 patients and the potential role of PSMA overexpression as a biomarker for neoangiogenesis, in both oncological and infective disorders.

Keywords: COVID-19, PET/CT, prostate cancer, PSMA, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) has caused an unprecedented global pandemic considerably affecting the care and well-being of cancer patients [1]. COVID-19 is generally presenting with interstitial pneumonia. However, a more specific pattern of COVID-19 is related to the vascular changes associated with the disease. The amount of new vessels growth is predominantly based on a mechanism of intussusceptive angiogenesis. This angiogenic process was more than two folds higher compared to H1N1 related influenza [2].

The standard of reference for confirming COVID-19 relies on real-time polymerase chain reaction (RT-PCR) using nasopharyngeal swab [3]. Serology tests also bring an added value to detect infected patients, namely those presenting with asymptomatic disease [4]. Moreover, chest-CT may lead to an early detection

of COVID-19 related interstitial pneumonia, especially in patients with negative RT-PCR. The main CT feature is the presence of ground-glass opacities (GGO), with a typical peripheral, subpleural and bilateral distribution [5]. RT-PCR false positive and false negative results have harmful consequences, especially in cancer patients, leading to contextualize the result together with both the clinical and the radiological picture of each patient, and to develop new diagnostic strategies [6].

COVID-19 related mortality in oncological patients is significant [7] and PET imaging holds a limited role in the management of COVID-19 patients. However, several case reports already described lung uptake of several PET radiopharmaceuticals [8-11]. Prostate-Specific Membrane Antigen (PSMA) is a type II transmembrane protein up regulated in prostate cancer (PCa) cells and in several other conditions, including angiogenesis [12, 13]. At present, ^{68}Ga-PSMA-11 PET/CT is one of the leading imaging procedures to investigate PCa. Thus, cases of COVID-19 pneumonia have been incidentally observed in PCa patients referred to ^{68}Ga-PSMA-11 PET/CT [9-11]. There is a clinical need to understand ^{68}Ga-PSMA-11 uptake patterns in patients with COVID-19 as well as to assess its potential value as an imaging biomarker for neoangiogenesis in both oncological and infective disorders (e.g. COVID-19).

Therefore, the aim of this case series was to explore pulmonary PSMA expression not related to PCa in patients with concomitant COVID-19 who underwent ^{68}Ga-PSMA-11 PET/CT to investigate PCa.

Materials and methods

Study design and patient population

Between March 2020 and October 2020, clinical, pathological, and imaging data from seven Nuclear Medicine PET Centers [Bologna, Parma and Turin (Italy), Campinas, Recife and Rio de Janeiro (Brazil) and Brussels (Belgium)] were retrospectively reviewed and collected. Inclusion criteria were: a) ^{68}Ga-PSMA-11 PET/CT performed for PCa; b) concurrent RT-PCR and/or follow-up serology (IgM and IgG) proven COVID-19 infection; c) time between ^{68}Ga-PSMA-11 PET/CT and COVID-19 confirmation less than 6 weeks; d) informed consent form signed. Patients with inconclusive or uncertain RT-PCR and/or serology were excluded. In all centers involved, RT-PCR and serologic test were performed in accordance with procedural guidelines for COVID-19. A formal IRB approval regarding this case-series analysis has been waived by the ethical committee of the promoting institution (IRCCS Azienda Ospedaliero-Universitaria di Bologna).

Imaging procedures and interpretation

All ^{68}Ga-PSMA-11 PET procedures included in this case series were performed according to procedure guidelines [14]. No significant differences in CT study protocol were reported. All PET/CT were performed using non-contrast enhanced, low-dose CT, without breath-hold protocols. Anonymized CT datasets were evaluated by a radiologist with extensive experience in COVID-19 imaging (CM), according with Radiological Society of North America (RSNA) recommendation [15]. Anonymized PET imaging datasets were evaluated independently by two experienced nuclear medicine physicians (ST, AF). Disagreements were solved by consensus. Images were interpreted visually and applying semi-quantitative analysis. ^{68}Ga-PSMA-11 positive regions were evaluated drawing volume of interest (VOI) of 3 cm^3 over areas of lung parenchyma with increased uptake in relation to the surrounding lung parenchyma. Maximum standardized-uptake-value (SUV_{max}) was calculated as the hottest voxel within the VOI. Blood-pool SUV_{max} (thoracic aorta) and liver SUV_{max} (right lobe) for each patient were calculated. Patients were stratified according to SUVmax in lung lesions suspected for COVID-19 alterations: SUV_{max}-Lung < SUV_{max}-Blood pool (low uptake); SUV_{max}-Blood pool < SUV_{max}-Lung < SUV_{max}-Liver (mild-to-moderate uptake); SUV_{max}-Lung > SUV_{max}-Liver (high uptake). CT alterations and PET abnormalities were visually compared to define areas of match/mismatch.

Results

Nine patients were included in this analysis (median age 64 years, range 51-75 years). Six out of 9 (67%) patients were diagnosed through RT-PCR, while 3/9 (33%) patients by serology (1/3 IgM; 2/3 IgG). In IgG+ patients, serology diagnosis was performed after imag-

Table 1. Patient characteristics

ID	Group	Age (years)	Clinical Setting	Concurrent Therapy for PCa	ISUP grading	PSA at PET (ng/mL)	PET result for PCa	Pulmonary PSMA uptake	GGO SUVmax	Pulmonary CT findings	RSNA Classification	Correspondence PSMA uptake - CT alterations	COVID-19 confirmation	COVID-19 symptoms
01	1	66	Primary staging	None	4	21.6	T	Mild bilateral uptake (++ in right peripheral)	1.6	Multifocal, diffuse, bilateral and peripheral GGO	Typical appearance	Yes	Serology	No
02	1	51	CRPC	AR-targeted therapy	5	24.3	M1a, b, c (lung)	Mild in right lobe Multiple bilateral areas of focal and high uptake classified as lung metastases	2.0	Peripheral GGO in the superior right lobe Multiple bilateral lung nodules classified as lung metastases	Typical appearance	Mismatch between uptake areas and CT alteration areas	RT-PCR	Fever; cough
03	2	56	BCR	None	5	2.6	M1b	Moderate, bilateral, diffuse, peripheral	3.5	Bilateral, basal and peripheral GGO	Typical appearance	Yes	RT-PCR	Fever; cough
04	2	65	BCR	None	3	0.5	negative	Moderate bilateral diffuse peripheral (++ right lung)	3.1	Multifocal, bilateral and peripheral GGO in all lobes (++ right lobe)	Typical appearance	Yes	RT-PCR	Fever; cough; fatigue
05	2	74	BCR	None	3	0.7	negative	Mild, basal, bilateral	2.1	Peripheral and multifocal GGO in right lobes with crazy paving and vascular dilations.	Typical appearance	Yes	Serology	Fatigue
06	2	75	BCR	None	5	0.1	negative	Moderate diffuse (++ in peripheral lower right lobe)	3.1	Peripheral ground GGO in the lower right lobe	Typical appearance	Yes	RT-PCR	Fever; cough; muscle pain
07	2	64	Primary staging	None	7	9.5	T3, N0, M0	Moderate bilateral (++ lung)	2.9	Multifocal, bilateral, and peripheral GGO, with crazy paving and vascular dilations	Typical appearance	Yes	RT-PCR	Cough; dyspnea
08	2	68	CRPC	LH-RH analogue	na	11.0	M1b	Moderate, peripheral bilateral	2.5	GGO in all lobes, with crazy paving	Typical appearance	Some small GGO without PSMA uptake	RT-PCR	Odynophagia
09	3	62	BCR	None	5	0.3	negative	Intense tracer uptake in both lungs	4.0	Subpleural bands and architectural distortion in the superior lobes; vascular dilatations; GGO in the lower right lobe	Typical appearance	Yes	Serology	Anosmia; fatigue

Notes: PCa = prostate cancer; ISUP = International Society of Urological Pathology; GGO = ground glass opacity; CRPC = castration-resistant prostate cancer; BCR = biochemical recurrence; AR = androgen receptor; RT-PCR = real-time polymerase chain reaction.

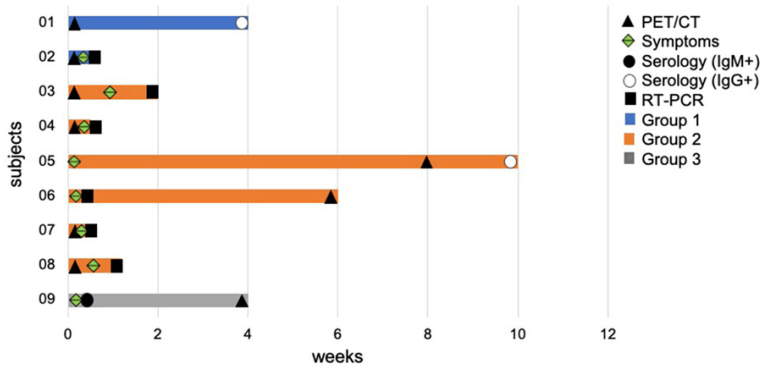

Figure 1. Swimmer plot. Each bar represents one patient.

ing findings of interstitial pneumonia and/or symptoms, suggestive for COVID-19 infection. In 7/9 (78%) patients COVID-19 diagnosis was proved after incidental findings at PET/CT, while 2/9 (22%) were referred to PET/CT as confirmed COVID-19 positive patients. In all PET scans ^{68}Ga-PSMA-11 abnormal lung uptake was observed, corresponding to CT COVID-19 alterations in 7/9 (78%) patients, while in 2/9 (22%) patients ^{68}Ga-PSMA-11 uptake was not matching exactly CT alterations. Ground glass areas with ^{68}Ga-PSMA-11 uptake showed a median maximum axial diameter on CT images of 11.2 mm (IQR: 1.7-18.4 mm), while ground glass areas without ^{68}Ga-PSMA-11 uptake had a median maximum diameter of 8.6 mm (IQR: 1.5-9.4 mm). Median SUVmax of the ground glass areas was 2.9 (IQR 2.1-3.1). Median SUVmax of the liver (right lobe) was 4.9 (IQR 3.9-5.0) whereas median SUVmax of the blood-pool (thoracic aorta) 1.7 (IQR 1.4-2.0). According to RSNA COVID-19 recommendations, 9/9 (100%) were classified as typical. Only one patient (patient-02) showed bilateral lung nodules PSMA-positive already classified as metastases related to PCa at previous HRCT scans in addition to the peripheral GGO in the superior right lobe. Patient population characteristics are reported in **Table 1** and **Figure 1**.

Sub-population analysis

Two of 9 (22%) patients showed faint ^{68}Ga-PSMA-11 uptake within the lung (low uptake). Patient-01 had bilateral areas of faint ^{68}Ga-PSMA-11 uptake matching with GGO alterations in CT. Patient-02 showed areas of faint uptake not matching with GGO. Subsequently, he showed symptoms (fever and cough), and COVID-19 infection was confirmed by RT-PCR. New areas of GGO were visible in the HRCT subsequently performed during hospitalization and not matching with previous ^{68}Ga-PSMA-11 uptake. 6/9 (67%) patients had lung ^{68}Ga-PSMA-11 uptake higher than the blood-pool, but below the liver (mild-to-moderate uptake). Areas of mild ^{68}Ga-PSMA-11 uptake within the lung matching with CT alterations were observed in 5 patients, while mismatch was observed in one patient. Patients-03 and 04 were asymptomatic when underwent ^{68}Ga-PSMA-11 PET/CT and developed symptoms after a few days with subsequent COVID-19 infection confirmation. Patients-05 and 06 underwent ^{68}Ga-PSMA-11 PET/CT within 6 weeks after COVID-19 symptoms appearance. Patient-07 had cough and dyspnea attributed to his chronic obstructive respiratory disease due to heavy smoking habits. After the scan he promptly underwent RT-PCR which had a positive result and he was subsequently admitted in intensive care unit after worsening of clinical condition. A mismatch between PSMA expression and CT alterations was observed in patient-08, who had small GGO areas (< 1.5 cm) without ^{68}Ga-PSMA-11 uptake (**Figure 2**). One out of nine (11%) presented intense uptake of ^{68}Ga-PSMA-11 lung uptake in both lungs corresponding to GGO areas. The serologic test, performed 4 weeks before PET/CT, showed negative IgG but positive IgM and HRCT revealed the presence of interstitial pneumonia (**Figure 3**).

Discussion

PSMA is physiologically up-regulated in tumor-associated neovasculature and in inflammatory and infectious processes [12, 13]. Nevertheless, PSMA expression has not been reported in endothelial cells of normal tissues. However, even if the presence of increased neo-angiogenesis at the level of lung interstitial tissue has recently been confirmed in patients affected by SARS-CoV-2, compared to patients with H1N1 influenza and healthy subjects without lung diseases [2], the mechanism of PSMA uptake within the lungs for COVID-19 patients has not been investigated yet. Hypothesis ranging from an increased availability of PSMA ligand to the site of inflammation/infection due to an increase in

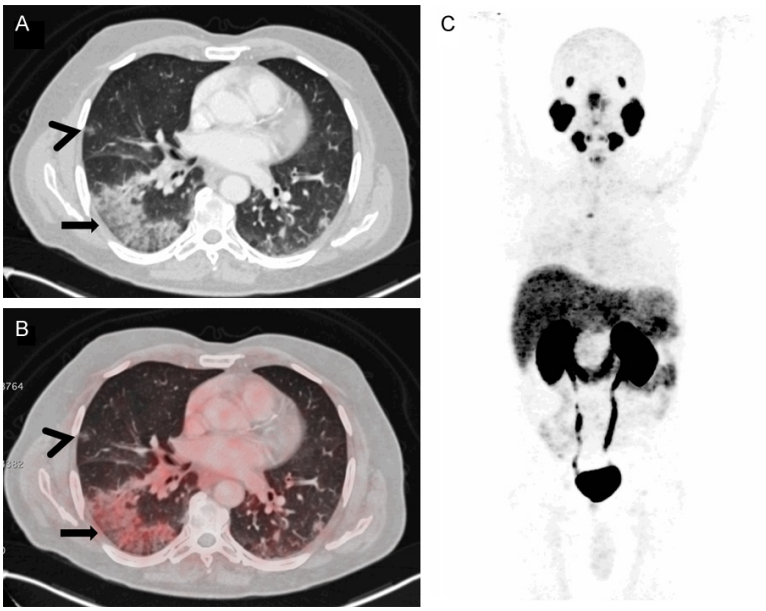

Figure 2. Mild-to-moderate uptake, patient-08. CT (A) fused axial images (B) and MIP (C) of ^{68}Ga-PSMA-11-PET/CT showing GGO with crazy paving pattern corresponding to moderate tracer uptake (arrow) and a small area of GGO that doesn't show significant uptake (arrowhead).

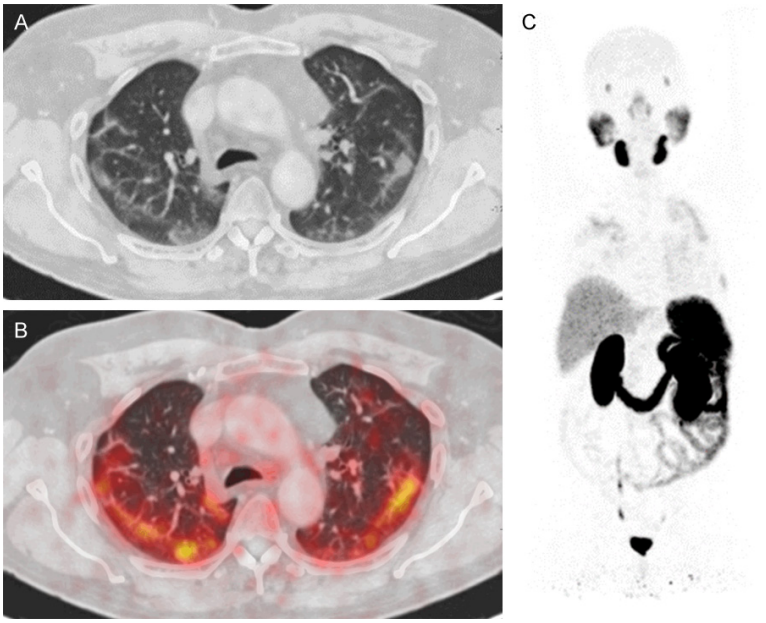

Figure 3. Intense Uptake, patient 9. ^{68}Ga-PSMA-11-PET/CT showing subpleural bands and architectural distortion in the superior lobes (A) corresponding to intense tracer uptake (B, C).

regional blood flow/vascular permeability or to an up-regulation in infection-associated neovasculature need confirmation.

In this case series we present data of 9 patients with ^{68}Ga-PSMA-11-PET/CT performed to investigate PCa and concurrent known or unknown COVID-19 infection. We described a heterogeneous pattern of PSMA-uptake within the lung, with most patients showing mild-to-moderate ^{68}Ga-PSMA-11 uptake. Interestingly, the most frequent pattern observed was a bilateral and posterior/peripheral lung involvement in accordance with typical COVID-19 pneumonia presentation. Furthermore, ^{68}Ga-PSMA-11 uptake was described in the lungs of 5/9 patients before the appearance of COVID-19 related symptoms. In most of the cases (77%) a matching between ^{68}Ga-PSMA-11 uptake and areas of GGO was observed. In two patients this condition was not observed: in one case areas of mild ^{68}Ga-PSMA-11 uptake did not correspond to GGO on CT, and in one case small nodular GGO areas did not show ^{68}Ga-PSMA-11 uptake, probably in relation to the small nodules dimension. To our knowledge, this is the first case series reporting ^{68}Ga-PSMA-11 in patients with concomitant SARS-CoV-2 infection. With current high prevalence of COVID-19 infection, our preliminary results suggest that ^{68}Ga-PSMA-11 PET/CT incidental findings in the lungs not related to PCa, namely in case of GGO with typical COVID-19 features in CT, as described by RSNA recommendation [15], might have a role in COVID-19 patients management, although further studies are needed to determine it, at least it raises red flags for a potential infection, if unknown.

The rate of COVID-19 testing continues to increase worldwide including asymptomatic individuals. There is the need to identify strate-

gies for early detection of COVID-19 cases in oncological asymptomatic patients. Our results suggest a potential correlation between PSMA uptake and COVID-19 pneumonia. Whether the source of this association relies on neoangiogenesis with consequent PSMA hyper-expression still needs to be clarified. Further studies, including dedicated histopathology assessment, are needed to confirm this hypothesis.

Limitations of our case series include the small sample size, the retrospective design, the lack of histopathological confirmation and the heterogeneity of COVID-19 validation tests. Furthermore, ^{68}Ga-PSMA-11 PET/CT was performed in different stages during the natural history of COVID-19 disease. This condition might have contributed to the different pattern of PSMA expression observed but represents the real-world scenario that many nuclear medicine units are facing during this pandemic.

Conclusion

^{68}Ga-PSMA-11-PET/CT detected increased PSMA uptake within the lung and not related to PCa matching with CT typical COVID-19 patterns in almost all patients. ^{68}Ga-PSMA-11 PET signal combined with CT features typical of COVID-19 pneumonia is highly suspicious for active infection, recommending serological or swab confirmation to improve patient management. Further studies are needed to evaluate the role of ^{68}Ga-PSMA-11 PET in COVID-19 patients and the potential role of PSMA overexpression as a biomarker for neoangiogenesis, in both oncological and infective disorders.

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Disclosure of conflict of interest

None.

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