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Invited Perspective

New wine in old bottles: ^{68}Ga-PSMA-11 PET/CT reveals COVID-19 in patients with prostate cancer

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Abstract: The COVID-19 pandemic continues to influence every aspect of human life across the globe. It was reported that vascular angiogenesis of COVID-19 was elevated in patients with equally severe influenza virus infection. In this issue of AJNMMI, Farolfi et al. reported that there was lung uptake not related to prostate cancer in almost all COVID-19 patients who performed ^{68}Ga-PSMA-11 PET/CT scans and most of the lung uptake lesions were matched with typical CT patterns of COVID-19. With the advantages of having various tracers for whole-body imaging, PET provides opportunities to study the mechanism of COVID-19 from different aspects and obtain patterns of extrapulmonary lesions in COVID-19, which helps explore more effective treatments for the patients. This case series opened the door to many future studies. Furthermore, such a multi-national/multi-institutional collaboration in the pandemic truly encouraged us that science is indeed without borders.

Keywords: Coronavirus Disease 2019 (COVID-19), prostate-specific membrane antigen (PSMA), positron emission tomography (PET), nuclear medicine, angiogenesis

Introduction

The COVID-19 pandemic continues to influence every aspect of human life across the globe [1]. As we know, the development of COVID-19 is identified with four stages: the first stage is characterized by upper respiratory infection; the second by the onset of dyspnea and pneumonia; the third by complications, including acute respiratory distress syndrome (ARDS), acute cardiac and kidney injury, sepsis, and secondary infection; and the fourth by exitus or healing [2]. For the treatment of COVID-19 patients, antiviral agents are, to some extent, effective to inhibit the clinical progression and complications of COVID-19 [3]. Immunomodulatory drugs, especially inflammation inhibitors, are helpful to treat COVID-19 patients in advanced stages [4]. The World Health Organization published the trial results in February 2021 and declared that these remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on reducing the overall mortality, initiation of ventilation, or hospital stays of hospitalized patients with COVID-19 [5]. Hence, further studies are still needed to identify the mechanism and explore more effective treatments for COVID-19 patients to prevent the virus replication and reduce the mortality and the rate of severe pneumonia.

It was reported that vascular angiogenesis of COVID-19 was much higher than that of equally severe influenza virus infection [6]. Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein and well-known to be overexpressed in prostate cancer (PCa). PSMA expression has been reported to be related to several benign and malignant diseases, especially with angiogenesis in tumor-associated endothelium [7, 8].

^{68}Ga-PSMA-11 is commonly used for PSMA targeted PET imaging [9]. In this issue of *American Journal of Nuclear Medicine and Molecular Imaging*, Farolfi *et al*. reported that there was lung uptake not related to PCa in almost all

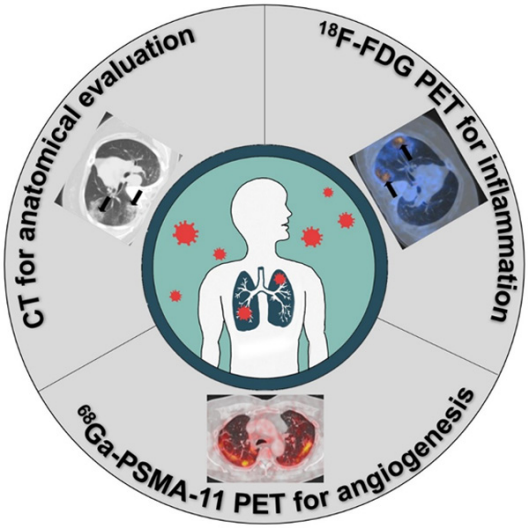

Figure 1. CT, ^{18}F-FDG PET, and ^{68}Ga-PSMA-11 PET imaging of COVID-19. Each imaging modality reveals different aspect of the virus from its infection to progression. CT image and ^{18}F-FDG PET/CT image adapted with permission from Ref. 11; ^{68}Ga-PSMA-11 PET/CT image adapted with permission from Ref. 10.

COVID-19 patients who had ^{68}Ga-PSMA-11 PET/CT scans and most of the lung uptake lesions were matched with CT typical COVID-19 patterns [10]. They divided nine patients into three groups according to the SUVmax of the lung uptake of ^{68}Ga-PSMA-11. Most of the patients (6/9) showed moderate lung uptake, which was higher than the blood poor and lower than the liver uptake. In this group, five of the patients were confirmed COVID-19 positive by the RT-PCR and showed typical COVID-19 symptoms, and the other one was confirmed by the serology. There was a patient in the moderate group showing mismatched lung uptake and ground-glass opacities (GGO) in CT, which may be due to the small size of the GGO areas. Two patients showed low lung uptake of ^{68}Ga-PSMA-11 and one of them showed no match with GGO in the CT. It was noticed that this patient showed typical symptoms (fever and cough) and was confirmed to have COVID-19 after the PET/CT scan. It is interesting to note that one patient showed high, peripheral, and bilateral lung uptake of ^{68}Ga-PSMA-11, while also having negative IgG but positive IgM in the serologic test 4 weeks before the PET/CT scan. Further study is needed to confirm the different lung uptake patterns of ^{68}Ga-PSMA-11 in different COVID-19 stages, including the early or asymptomatic stage.

To date, many studies have reported PET/CT images of COVID-19, but most of them used ^{18}F-FDG [11, 12]. Farolfi *et al*. inspired us to focus on the lung uptake patterns of different PET agents in COVID-19 patients (**Figure 1**) [10]. There are many other angiogenesis-related PET imaging agents [13, 14]. A group of promising neoangiogenesis-related PET imaging agents is the radiolabeled inhibitors against fibroblast activation protein (FAP), such as ^{68}Ga-FAPI [15]. FAP is overexpressed in tumor-associated fibroblasts and contributes to matrix remodeling, angiogenesis, immune evasion, and drug resistance [16]. Several kinds of prevalent cancers are reported to present remarkably high uptake and image contrast on ^{68}Ga-FAPI PET/CT [17]. Is there any possibility to observe lesion uptake of ^{68}Ga-FAPI in neoangiogenesis-related diseases other than tumors, for instance COVID-19?

SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) as the entry receptor [18, 19]. However, ACE2 expression is not limited to the lung but it is also in multiple extrapulmonary tissues [20]. As reported, SARS-CoV-2 can result in several extrapulmonary manifestations, including neurologic, cardiac, hepatic, endocrine, gastrointestinal, and renal dysfunction [20, 21]. One of the advantages of PET imaging is that it can perform whole-body imaging. Could the extrapulmonary lesions have any uptake of radiolabeled PET agents over the whole body of COVID-19 patients? What are the patterns of extrapulmonary lesions imaging?

Although we already know about the four clinical stages of COVID-19, the pathophysiology and pathology of the disease are remaining to be further explored. As we know more about the mechanism and development of COVID-19 infection, we will find more precise treatments for COVID-19 patients and reduce the mortality and the rate of severe pneumonia. As it is reported that COVID-19 is associated with neoangiogenesis, could the anti-neoangiogenesis agents be valuable to the treatment of COVID-19? These questions remain to be answered.

So far, most of the studies have used ^{68}Ga-PSMA-11 to detect tumor-associated angiogenesis [22, 23]. There are still many other diseases that are related to neoangiogenesis, including fibrous dysplasia, osteoarthritis, diabetic

retinopathy, diabetic kidney disease, sarcoidosis, cardiac remodeling, and COVID-19 according to the latest reports [6, 24]. Several cases were reported suggesting that there was lesion uptake of ^{68}Ga-PSMA-11 in neoangiogenesis-related diseases, including multiple myeloma [25], osteosarcoma [26], and follicular thyroid adenoma [27]. These cases indicated that ^{68}Ga-PSMA-11 is not only a PCa imaging agent, but also has the potential to diagnose other neoangiogenesis-related diseases, as well as to predict and monitor the antiangiogenesis-based therapeutic efficacy.

Overall, Farolfi *et al*. reported for the first time that ^{68}Ga-PSMA-11 PET/CT detected increased lung uptake, which is not related to PCa and matched with CT typical COVID-19 patterns in almost all patients [10]. Although there are some limitations of the small sample size and the lack of histopathological confirmation, this study encourages us to evaluate COVID-19 patients from a different perspective and indicates the potential of PSMA overexpression as a biomarker with ^{68}Ga-PSMA-11 as an indicator for the diagnosis and therapy monitoring of neoangiogenesis-related diseases, including oncology and inflammation.

Some interesting questions remain to be studied: 1) Could we use PET agents other than ^{18}F-FDG and ^{68}Ga-PSMA-11 to image lesions of COVID-19 patients, such as ^{68}Ga-FAPI? 2) Could the extrapulmonary lesions have any uptake of PET agents over the whole body of COVID-19 patients? 3) What are the patterns of extrapulmonary lesions imaging? 4) Could the anti-neoangiogenesis agents be valuable to the treatment of COVID-19? 5) Could ^{68}Ga-PSMA-11 have the potential to diagnose neoangiogenesis-related diseases other than tumors?

The last year and a half have collectively been perhaps one of the most difficult times in our lifetimes. This work on the use of ^{68}Ga-PSMA-11 PET/CT in COVID-19 patients with prostate cancer is important from a scientific perspective, but also because it has demonstrated that scientists, clinicians, technologists, radiochemists, oncologists, etc. around the globe (in this case four countries: Brazil, Italy, Belgium, and Germany) can unite during these extremely challenging times to fight against a common enemy of the human race, the corona virus. The major limitation of this study is the small sample size, which is a consequence of various complications. Nevertheless, this case series is the first study of its kind and has hopefully opened the door to many future studies. Such a multi-national/multi-institutional collaboration in the pandemic is truly uplifting and inspirational. It has clearly demonstrated that science is indeed without borders, for we all live in the same one world.

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Disclosure of conflict of interest

Weibo Cai is a scientific advisor, stockholder, and grantee of Focus-X Therapeutics, Inc. All other authors declare no conflict of interest.

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