Editorial

PET in the diagnostic management of infectious/inflammatory pulmonary pathologies: a revisit in the era of COVID-19

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Introduction

Inflammatory and infectious pulmonary diseases represent a significant cause of morbidity and mortality. Different morphological imaging techniques, and mainly computed tomography (CT), have been employed to study lung inflammation. However, these techniques suffer from limitations, such as suboptimal sensitivity or specificity.

More recently, molecular imaging and nuclear medicine modalities, such as single-photon emission computed tomography and PET, have been shown to provide high sensitivity in detecting pulmonary infection and inflammation. Specifically, PET results in accurate detection and optimal physiologic monitoring of disease activity. Moreover, the addition of CT to PET images provides both structural information and functional/molecular data. In fact, ^{18}F-fluorodeoxyglucose (FDG) PET coupled with CT has been proved to be very useful in various inflammatory and infectious disorders with many recent efforts expanding its clinical applications [1].

The ability of FDG-PET to identify infection and inflammation basically relies on the same pathophysiologic mechanism as malignancies, which is an elevated glycolytic activity and cellular metabolism involved in the inflammatory response. The increased uptake of FDG by the inflammatory cells is mainly related to high levels of glucose transporters and hexokinase activity expressed by the inflammatory cells [2].

The usefulness of FDG-PET/CT in the diagnosis and management of various infections and inflammatory lung diseases has been widely reported [1,3]. In this article, we aim to review the diagnostic performance of FDG-PET/CT in non-neoplastic pulmonary diseases.

Coronavirus disease 2019

Novel coronavirus disease 2019 (COVID-19), an emerging respiratory infection first reported in Wuhan (China), has attracted intense attention all around the world. Since 30 January 2020, COVID-19 has been declared as a public health emergency by the WHO, with new cases emerging rapidly worldwide. By 29 August 2020, a total of 25 million COVID-19 cases with more than 840 000 deaths have been confirmed [4]. The majority of infected patients present with fever and cough and mostly represent bilateral multifocal pulmonary lesions. No definitive treatment for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection exists to date. Hence, early detection and isolation, and appropriate conservative treatments remain to be the basic most effective strategies to fight against the COVID-19 outbreak.

The gold standard diagnosis is based on viral RNA nucleic acid testing (RT-PCR); however, false-negative results are not uncommon. Consequently, high-resolution CT chest has been introduced as another diagnostic modality for COVID-19 [5]. Chest CT scan is useful not only in the initial diagnosis of COVID-19 but also in monitoring disease progression and response to treatment. Chest CT imaging characteristics vary in different cases and stages of the disease. Multifocal bilateral pulmonary ground-glass opacities with a subpleural/peripheral distribution have been reported to be the earliest and most typical CT manifestation in COVID-19. With disease progression, superimposition of consolidation on ground-glass opacities is seen. Other imaging manifestations of SARS-CoV-2 infection include reticular pattern with interlobular septal thickening accompanied by possible pulmonary vascular enlargement, air bronchogram sign crazy paving pattern [6]. Pleural and pericardial effusion, pulmonary cavity formation, and mediastinal lymphadenopathy are considered atypical for COVID-19 [7]. Although several typical and atypical CT features have the disease have been described, in general, CT is a nonspecific imaging modality for the diagnosis of atypical types of pneumonia.

Although ^{18}F-FDG-PET/CT is not routinely applied in an emergency setting and specifically for the diagnosis of types of pneumonia, its potential clinical value in pulmonary inflammatory/infectious conditions has already been shown [1,3]. Also, incidental detection of COVID-19 on PET/CT has been recently reported (Fig. 1). A

Fig. 1
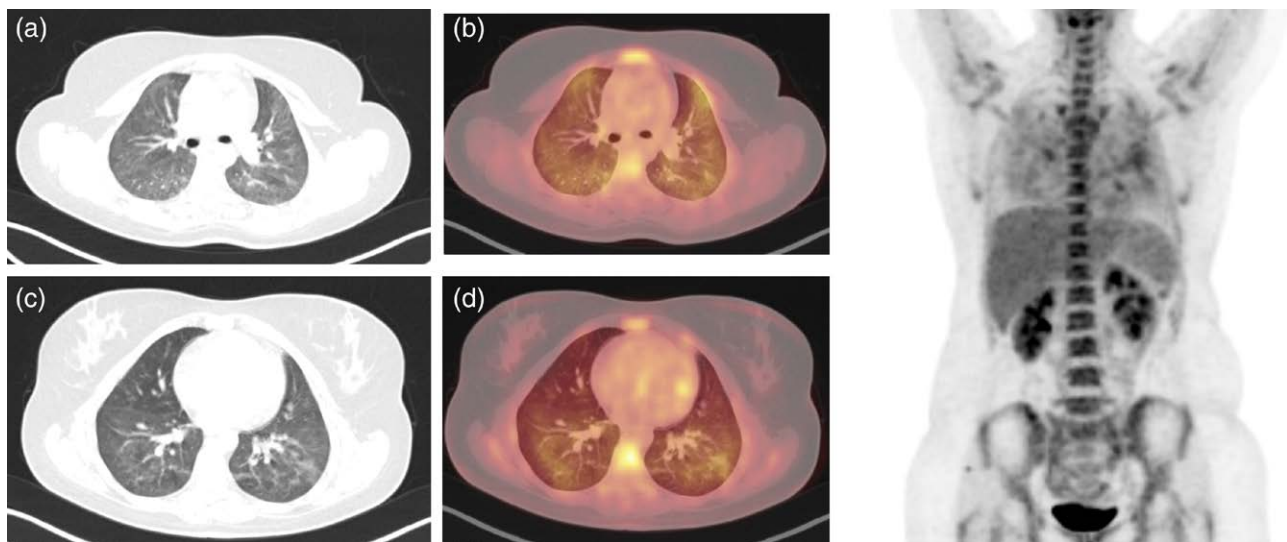
FDG PET/CT findings in a COVID-19 patient. A 56-year-old woman with history of dry cough and intermittent fever presented for FDG-PET/CT to evaluate metastatic breast cancer. Maximum intensity projection image (MIP) demonstrates diffuse bilateral increased metabolic activity of the lungs. Low-resolution chest CT shows subpleural peripheral ground-glass opacities (a, c). PET/CT also demonstrate increased pulmonary FDG uptake in the dependent segments of bilateral lungs (b, d). CT, computed tomography; COVID-19, coronavirus disease 2019; FDG, fluorodeoxyglucose.

retrospective review regarding FDG-PET/CT findings in four suspected COVID-19 cases found characteristic peripheral ground-glass opacities with high FDG avidity along with increased nodal FDG uptake, which is in favor of reactive lymphadenitis [8]. In another case study [9], a 55-year-old male smoker with intermittent fever, fatigue, and dry cough in Wuhan underwent chest CT-scan which suggested lung hilar malignancy. Consequently, FDG-PET/CT was performed, which demonstrated multifocal hypermetabolic pulmonary lesions accompanied by right paratracheal and right hilar FDG-avid lymph nodes. Subsequently, the patient confirmed to have COVID-19 pneumonia by RT-PCR.

Similar to other respiratory viral infections, FDG-PET/CT holds a potential complementary role in COVID-19 pneumonia to offer for the emerging novel targeted antiviral therapies. More importantly, COVID-19 demonstrates several extrapulmonary involvements, such as gastrointestinal inflammation, which can be detected in PET/CT whole-body imaging. Interestingly, as shown in Fig. 1, PET/CT could sometimes demonstrate additional sites of active disease, compared to the conventional CT scan. Indeed, carrying additional information regarding the metabolic changes at cellular level, PET/CT might detect disease before showing up on other imaging tests. It should be noted that PET/CT is neither the first-choice modality for diagnosis of COVID-19 nor a technique for screening purposes. However, our review stresses that this disease should be placed among the differential considerations in patients with bilateral multifocal increased FDG uptake. In the event of diagnosis such cases, this is

the responsibility of the reading nuclear medicine physician or radiologist to inform the referring clinician, not only to guide appropriate patient management but also about possible post-exposure recommendations. The radiology department staff should be notified as well for possible post-exposure recommendations. These days, due to the high prevalence of the disease, the nuclear medicine department staff should be educated about precautions and safety measures to manage patients with known or suspected NCIP. In epidemic areas, all nonemergent nuclear medicine examinations should be postponed, not only for the safety of staff but also to minimize the potential nosocomial spread of the disease.

Other respiratory viral infections

Viral pathogens are the most common causes of respiratory infection, such as influenza, human parainfluenza virus, respiratory syncytial virus, rhinovirus, and adenovirus. Besides, the occasional emergence of novel respiratory viral infections has been associated with regional outbreaks, such as H5N1 avian influenza in Southeast Asia, the epidemic of SARS, Middle East respiratory syndrome, and the pandemic of swine-origin H1N1 influenza that began in early 2009.

Generally speaking, chest radiography and computed tomography (CT) are the preferred methods to characterize pulmonary morphologic changes at the time of presentation and also to monitor treatment efficacy and disease progression. CT features of various respiratory viral pathogens have been widely described in literature [10]. These imaging findings are diverse and sometimes mimic those

of other nonviral infectious and inflammatory diseases. Diffuse ill-defined patchy ground-glass opacities, consolidation, and interlobular septal thickening are some of the most common manifestations that have been frequently reported. However, despite their clinical usefulness for patient management, radiographic methods are nonspecific and unable to illustrate the underlying pathologic mechanisms. Molecular imaging methods, and particularly PET, illustrate the behavior of inflammatory cells in their native microenvironment. Increased FDG uptake in the acute pulmonary inflammation/infection occurs because of the activated neutrophils, whose metabolism is heavily dependent on anaerobic glycolysis [3]. Therefore, PET/CT can provide quantification of the inflammatory process throughout the lung fields. Previous studies of human and non-human experimental models revealed that acute inflammatory responses play a critical role in the severe respiratory dysfunction induced by the H1N1 and the H5N1 avian influenza viruses and by the SARS coronavirus [11,12]. FDG-PET offers great potential to study the inflammatory response to respiratory viral infections [11]. Bellani *et al.* study on the role of FDG-PET/CT in severe influenza revealed increased tracer uptake corresponding to pulmonary ground-glass opacities in CT images [12]. On the other hand, while there are still challenges in developing effective therapies in acute respiratory diseases, molecular imaging with PET can offer a potential added value in predicting disease progression by new biomarkers and may support the development of novel therapies targeting viral replication or damaging host responses.

Tuberculosis

Despite a global effort by health services, tuberculosis remains a global health issue, as one of the world's leading cause of infectious mortality. All body organs can potentially be involved by tuberculosis, but the lung is the most commonly involved organ.

In numerous studies, PET/CT has been demonstrated as an increasingly valuable tool for assessment of metabolic activity in tuberculous lesions [13–15]. PET identifies active granulomatous lesions with a high accuracy rate. Most commonly, due to activated inflammatory cells with high glycolytic metabolic rates, active tuberculous granulomatous lesions appear as intensely FDG-avid lesions on PET/CT images [13,14]. However, depending on the severity of inflammatory response, the lesions may display different uptake patterns, such as a central cold focus without significant confluent inflammatory reaction, in case of abscess formation, as reported by Yago *et al.* [15]. FDG-PET also provides the opportunity to delineate the extent of disease involvement with the detection of extrapulmonary sites of occult disease. Previous studies have confirmed that even in asymptomatic extrapulmonary disease, FDG-PET/CT is able to detect active tuberculosis, partly thanks to its whole body imaging properties [14]. In a pilot study, Sathekge *et al.*

[16] demonstrated that in HIV-negative patients affected by tuberculosis, FDG revealed more extensive involvement compared to contrast-enhanced CT scanning.

Soussan *et al.* [17] suggested two different patterns of tuberculosis based on FDG-PET appearance: the more common isolated pulmonary pattern and the more systemic lymphatic pattern. The potential ability of rapid evaluation of both pulmonary and extrapulmonary tuberculosis simultaneously by PET offers time-saving and cost-effectiveness opportunities.

On the other hand, FDG-PET/CT imaging can evaluate response to treatment during and after the treatment course. Morphological changes often take remarkably longer to be detectable than molecular changes. A recent systematic review and meta-analysis by Sjölander *et al.*, demonstrated PET ability for assessment of anti-tuberculosis therapy response and outcome in tuberculosis-infected patients, focusing on SUV-based response evaluation [18]. Another study by Demura [19] *et al.* demonstrated the usefulness of FDG-PET/CT in the diagnosis and monitoring of therapy for pulmonary mycobacteriosis. Davis *et al.* [20] showed the potential of this technique to monitor response to therapy in animals with tuberculous lesions, Namakoong *et al.* [21] recently published a case report on the value of FDG-PET/CT in assessing appropriate duration for anti-mycobacterial therapy in a patient with HIV infection.

Nontuberculous mycobacterial lung infections

Nontuberculous Mycobacteria (NTM) infections are caused by a diverse group of opportunistic mycobacterial pathogens. Few studies have reported FDG-PET/CT to be potentially useful in the management of NTM infections. FDG-PET/CT is able to detect both pulmonary, lymph node, and extrapulmonary extranodal involvement simultaneously in NTM lung infections. Similar to tuberculosis, the pulmonary nodular lesions of NTM (especially *Mycobacterium Avium* Complex) display high FDG uptake on PET images [22]. Ginevra Del Giudice *et al.* [23] demonstrated the potential added value of FDG-PET/CT in assessing the activity and extent of the disease, not only in nodular lesions but also within a broad range of radiologically visible lung lesions in NTM and tuberculosis. Also, they suggested differences in PET uptake between NTM and mycobacteriosis patients. They found that the average uptake values of lung lesions of NTM are lower than tuberculosis. However, In the study undertaken by Demura *et al.* the average uptake in patients with MAC was higher than those with tuberculosis [19]. This discrepancy indicates the need for further researches on this point.

Like tuberculosis, FDG-PET uptake can determine disease activity with higher accuracy compared to anatomic imaging. A study by Demura showed post-treatment

PET in MAC correlates with the disease state, despite the persistence of pulmonary lesions on CT [19].

In conclusion, despite some limitations and questionable uncertainties, the role of PET/CT imaging both in NTM and mycobacterial tuberculosis infections cannot be overemphasized, not only in assessing the extent and severity of disease activity but also in guiding the treatment and post-treatment follow-up.

Pulmonary fungal infections

The primary role of FDG-PET/CT in fungal infections relates to its ability to evaluate the extent of active disease. FDG-PET/CT also provides valuable metabolic information regarding monitoring response to antifungal treatments for optimal adjustment and/or termination of the treatment. Xu et al. [24] have demonstrated that changes in FDG uptake on PET (semiquantitatively defined as SUVmax) is a more accurate measure for disease activity compared to morphological changes in lesion size obtained from anatomic imaging. The authors also observed that an increase in SUVmax is associated with disease progression and vice versa. However, there are limited pieces of literature in this field and further studies are definitely warranted.

Candidiasis

The candidiasis lesions are shown to be FDG-avid on PET images [25]. However, FDG-PET role in guiding antifungal therapy in patients with candidiasis has not yet been fully explored. Xu et al. [24] suggested that FDG PET is able to offer accurate information on the therapeutic response in patients with chronic disseminated candidiasis undergoing antifungal therapy.

Pulmonary aspergillosis

The aspergillosis lesions usually show FDG-avidity on FDG-PET/CT. A great value of FDG-PET/CT in pulmonary aspergillosis is the ability to differentiate between invasive and noninvasive pulmonary aspergillosis [26]. While the invasive aspergillosis presents as multiple hypermetabolic nodules, the noninvasive aspergillosis presents as solitary metabolic nodules with a halo sign. The SUVmax is also higher for invasive aspergillosis variant. Furthermore, PET has been proven to be useful for therapy monitoring in patients with aspergillosis [27]. Novel PET tracers using ^{68}Ga-labeled compounds such as siderophores have also been offered for imaging of aspergillosis, but their effectiveness has not yet been fully understood [28].

Cryptococcus

A limited number of studies on the characteristic findings of PET in patients with cryptococcus revealed variable FDG avidity [29] Igai et al. [30] suggested that cryptococcus lesions can be mistaken as neoplastic pulmonary lesions. Therefore, these lesions should be kept in mind as differential considerations of false positivity of PET in the evaluation of malignant lesions.

Histoplasmosis

In pulmonary histoplasmosis infections, chest CT findings include consolidation in the acute form of the disease and sharply defined nodules in the chronic form [31]. Histoplasmosis lesions usually show FDG activity on PET images, and similar to other fungal infections, they could reduce the specificity of FDG-PET/CT for the detection of lung cancer in patients with solitary pulmonary nodules. Dual-time PET/CT has been suggested for differentiation between the benign and malignant lung and mediastinal lesions, especially in geographic areas with a high prevalence of benign conditions, such as histoplasmosis and sarcoidosis [31].

Coccidioidomycosis

Coccidioidomycosis infection mainly involves the lungs. These lesions show abnormal FDG uptake and may cause false-positive PET/CT findings in patients with suspected malignancy [32].

Blastomycosis

Based on limited available reports, pulmonary blastomycosis can have high FDG uptake and may mimic primary or metastatic lung malignancy on PET/CT. In a study on non-human models by Basset et al., SUV for *Blastomyces*-associated lesions are as high or higher than those of malignant lymphoma [33]. In addition, FDG-PET/CT in blastomycosis can unmask those sites of involvement that are not clinically apparent.

Mucormycosis

Dang et al. [34] showed a case of pulmonary mucormycosis presented as heterogeneous soft tissue mass with prominent peripheral FDG uptake.

Sarcoidosis

Sarcoidosis is a chronic multisystem inflammatory disease of unknown origin, characterized by the formation of noncaseating granuloma in lungs and various other organ systems. Precise assessment of inflammatory activity is critical for monitoring the course of the disease and guiding optimal treatment plan. However, establishing and quantifying inflammatory activity remains to be a challenge for clinicians. Recently, PET has been shown to be a very sensitive technique to assess inflammatory activity in the newly diagnosed symptomatic sarcoidosis patients by detecting and quantifying the level of inflammatory reactions in the lungs and other body organs [35]. Several articles demonstrated the potential role of PET/CT to evaluate the extent of disease in patients with sarcoidosis [36,37]. Several studies in known cases of sarcoidosis confirmed higher diagnostic accuracy of FDG-PET/CT compared to conventional 67-gallium scintigraphy [38]. Assessing active sarcoidosis by PET was even shown to

be more sensitive compared with serological markers of disease activity, such as angiotensin-converting enzyme [36].

Furthermore, within the realm of the diagnostic workup of sarcoidosis, PET study can uncover the most suitable target for biopsy to provide histological diagnostic evidence, particularly in patients with suspected sarcoidosis with insufficient evidence in bronchoalveolar lavage (BAL) and bronchoscopy. The valuable role of PET in identifying occult sites of the active disease has been shown in two cohort studies and several case reports [35,40]. Besides, positive PET findings in thoracic sarcoidosis are found to be associated with impaired lung function [37]. The role of FDG-PET /CT in other clinical indications, such as evaluation of treatment response and follow-up of patients with sarcoidosis has been also evaluated in several studies [39]. Lastly, FDG-PET also plays a significant role in assessing residual activity in patients with fibrotic pulmonary sarcoidosis [37], contributing to disease monitoring and treatment response evaluation. In terms of prognostic prediction, PET/CT seems to hold great importance in patients with sarcoidosis [37]. Also, a study by Kiatboonsri C [41] has shown FDG-PET ability to detect recurrent sarcoidosis in transplanted lungs.

Overall, FDG-PET and PET/CT appears to be a useful molecular imaging technique in staging, evaluating disease activity, monitoring treatment response, and prognostic evaluation in patients with sarcoidosis and may significantly influence the clinical management.

Miscellaneous pulmonary inflammatory disorders

FDG-PET/CT scan aids in characterizing various inflammatory conditions of lungs, including pneumonia [42], lung abscess [43], local allergen-invoked inflammation in asthma, and chronic obstructive pulmonary disease [44,45], cystic fibrosis [46,47], and acute lung injury/acute respiratory distress syndrome [46,48]. In asthma, as a noninvasive method, PET provides a highly predictive indicator of airway inflammation at a molecular/functional level. Consequently, it may efficiently assess the anti-inflammatory effects of novel therapeutic agents in order to provide excellent potential for advancing asthma research and development. In a study by Jones *et al.* [45], PET, as a potential marker of persistent lung inflammation, offered an assessment of the activity of lung inflammatory cells and assisted in the differentiation of COPD from asthma.

A case reported by Baha [49] revealed markedly elevated FDG uptake in a patient with concomitant pneumonia and squamous cell carcinoma. Similar SUVs were noted in both lesions. Neutrophil activity is considered responsible for increased FDG uptake in pneumonia. In cystic fibrosis, a study [47] found that higher numbers of neutrophils in BAL correlates positively with higher FDG uptake. Accordingly, FDG-PET was proposed to identify patients with more rapidly deteriorating lung function. Also, in patients with cystic fibrosis, an increased FDG uptake was seen in the upper lung zones in favor of greater pulmonary inflammatory involvement [46,47].

Summary

In patients with respiratory infectious/inflammations, molecular imaging methods such as PET would complement the conventional anatomic imaging techniques such as radiographs and CT by mapping the underlying pathophysiologic processes. PET will provide excellent information regarding the disease activity and will assist in predicting disease progression and will support the development of novel therapies targeting viral replication or host responses. Although the novel respiratory viral diseases, such as COVID-19, H1N1 influenza, and SARS, will inevitably continue to remerge, molecular imaging can help to reduce their impact on public health. It should be highlighted that PET/CT is not recommended in emergency settings; however, as a unique potent molecular method, it will offer a great chance to visualize the underlying inflammatory mechanism directly and assist the discovery of new biomarkers or novel therapies against these viral pathogens. Moreover, due to its ability to evaluate early metabolic changes at the cellular level, PET/CT might be a better marker of disease activity and extension in pulmonary infectious/inflammatory pathologies.

Acknowledgements

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