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FDG-PET/CT of COVID-19 and Other Lung Infections

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While not conventionally used as the first-line modality, [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography/computed tomography (PET/CT) can identify infection and inflammation both earlier and with higher sensitivity than anatomic imaging modalities [including chest X-ray (CXR), computed tomography (CT), and magnetic resonance imaging (MRI)]. The extent of inflammation and, conversely, recovery within the lungs, can be roughly quantified on FDG-PET/CT using maximum standardized uptake value (SUVmax) values. The Coronavirus disease 2019 (COVID-19) pandemic has highlighted the value of FDG-PET/CT in diagnosis, elucidation of acute pulmonary and extrapulmonary manifestations, and long-term follow up. Similarly, many other pulmonary infections such as previously documented coronaviruses, aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, and typical/atypical mycobacterial infections have all been identified and characterized using FDG-PET/CT imaging. The goal of this review is to summarize the actual and potential benefits of FDG-PET/CT in the imaging of COVID-19 and other lung infections. Further research is necessary to determine the best indications and clinical applications of FDG-PET/CT, improve its specificity, and ultimately ascertain how this modality can best be utilized in the diagnostic work up of infectious pathologies.
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Introduction

For decades, acute lower respiratory tract infections have been one of the three leading causes of mortality in both adult and pediatric populations, creating a substantial burden on the healthcare system. While standard radiologic imaging techniques, mainly chest X ray (CXR) and CT, are the primary imaging modalities to diagnose lung infection, FDG-PET/CT has proven to be effective in cases where conventional imaging falls short. Not only can metabolic imaging identify and track the infection earlier than other methodologies, but it can also provide vital information at the molecular level.[1,2] The high sensitivity of this modality coupled with wider anatomic coverage generates a more comprehensive and complete assessment of the patient's global disease burden, allowing for personalization of treatment strategy.

While the FDG-PET/CT imaging modality has primarily been reserved for imaging of malignancies, many authors have also recognized its value in non-neoplastic processes such as pulmonary infections. This is due to the fact that FDG acts as a glucose analogue, and thus gets taken up by the cell via glucose transporter 1(GLUT-1).[2] After cellular uptake, FDG is phosphorylated by the rate-limiting enzyme hexokinase, trapping FDG-6-phosphate in the cell.[2] This mechanism allows FDG-PET/CT to identify sites with increased glucose utilization and metabolism, which are non-specific but common markers of infection, inflammation, and malignancies.

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Ultimately, combining the functional aspects of FDG-PET/CT with the structural/anatomic facets of CT has the potential to revolutionize the diagnosis and treatment of pulmonary infections. While not normally utilized as a stand-alone methodology in infectious/inflammatory processes, FDG-PET/CT imaging has great utility when used in conjunction with other imaging techniques, as it provides additional information on the molecular level and can accurately quantify disease burden. This review aims to highlight the value of nuclear imaging in elucidating a variety of lung infections.

Mechanism of Localization of FDG in Inflammatory and Infectious Diseases

The introduction of PET/CT using FDG opens new areas of research in diagnosis of inflammatory and infectious diseases. FDG is a nonspecific tracer, and its level of uptake is proportional to the cellular metabolic rate and the density of glucose transporters, thus FDG accumulates at sites of infection and inflammation.[2-5] It is well established that inflammatory response, focal hyperemia, and increased vascular permeability are correlated with high uptake of FDG, with enhanced tissue blood perfusion leading to greater FDG delivery to the lesion site and local immune response resulting in release of proinflammatory cytokines and migration of inflammatory cells.[6,7] As activated inflammatory cells such as neutrophils, macrophages, lymphocytes, and fibroblasts significantly take up FDG, there is a direct correlation between the FDG uptake and the quantity of inflammatory cells in both acute and chronic inflammation where expression of active glucose transporters is upregulated.[8,9]

FDG avidity has been reported in the development of various pulmonary inflammatory and infectious diseases. In acute infection, FDG is absorbed mainly by activated parenchymal neutrophils, which are highly dependent on anaerobic glycolysis and demand high uptake of glucose. Therefore, FDG accumulates in the interstitial lung tissue and alveolar airspaces, permitting study of the behavior of inflammatory cells in their local microenvironment.[4,10]

COVID-19

Over the past year, the global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected over 170 million people worldwide, resulting in millions of patients developing pulmonary symptoms serious enough to require hospitalization and serial imaging. While reverse transcription-polymerase chain reaction (RT-PCR) CXR, and less commonly chest CT have been the primary tools of diagnosis, FDG-PET/CT may incidentally detect undiagnosed cases of COVID-19 in the early stages of infection, when symptoms are nonspecific. Recent studies have reported incidental FDG-PET/CT findings confirming COVID-19 in asymptomatic patients, including one series of 7 patients with 2 consecutive negative RT-PCR tests.[11] The authors found that the pulmonary lesions displayed significantly increased SUVmax (mean ± standard deviation, 3.44 ± 2.03 vs 0.54 ± 0.19) when compared to the lungs of control subjects.[11] In another study, FDG-PET/CT showed new lung infiltrates in asymptomatic patients roughly 7 days (range of 6.4 ± 7.8 days) prior to symptom onset.[12] Therefore, routine staging FDG-PET/CT scans may show incidental but typical imaging findings of COVID -19 and help initiate further workup (Fig. 1).

COVID-19 pneumonia is FDG avid, and numerous studies have documented lung uptake in both asymptomatic and symptomatic patients. As is typical on diagnostic CT, on FDG-PET/CT, ground glass opacifications (GGOs) with or without superimposed consolidation are appreciated in a peripheral, basilar, and posterior predominant pattern with increased metabolic activity.[13] Less intense uptake may be seen in lymph nodes and bone marrow.[14] In one of the earliest case reports of PET/CT imaging of COVID-19, Qin et al described 4 presumed cases with pulmonary involvement (a limitation of this case series being that SARS-CoV-2 nucleic acid testing was not done in 3 of the 4 and 1 case was PCR negative). However, at least 2 lobes showed SUVmax values ranging from 4.6 to 12.2 in areas that indicated GGOs on initial CT.[15] In 3 of the 4 cases, FDG-positive supraclavicular and mediastinal nodes were seen with SUVmax ranging between 5.4 and 7.[15] Zou et al[16] reported a case of suspected lung malignancy which after staging with FDG-PET/CT, revealed a right lung FDG-avid mass (SUVmax of 4.9) with additional uptake in the right paratracheal and hilar nodes as well as bone marrow (Fig. 2). Ultimately, the final diagnosis was COVID-19 confirmed by RT-PCR (Fig. 2).[16] Authors have also utilized FDG-PET/CT imaging to quantify the extent of inflammation in the lungs, due to the fact that nuclear imaging can detect inflammation even before anatomic changes are present. For instance, Dietz et al[17] classified COVID-19 induced inflammation based on hypermetabolic volume and SUVmax values; a low level of inflammation was classified by a hypermetabolic volume less than 50 mL and SUVmax less than 7, with any values above those levels considered a high level of inflammation. Therefore, FDG-PET/CT can be utilized in conjunction with clinical assessment to objectively determine the degree of disease severity.

Although there is no primary application for FDG-PET/CT in the diagnostic algorithm of patients with suspected COVID-19, there could be indications for metabolic imaging in the evaluation of residual disease and recovery. As part of the normal healing process, pulmonary infections may result in scar and/or organizing pneumonia, and continue to show radiographic abnormality, which may be indistinguishable from parent infection. This leads to longer and unnecessary follow-up imaging, while in reality, there are no active inflammatory lesions in the pulmonary parenchyma. In these instances, anatomic imaging modalities, including CXR and chest CT remain abnormal, while metabolic and functional imaging modalities, such as FDG-PET/CT, can accurately confirm the resolution of active inflammatory process.[18,19] Moreover, we emphasize the fact that the interpretation of

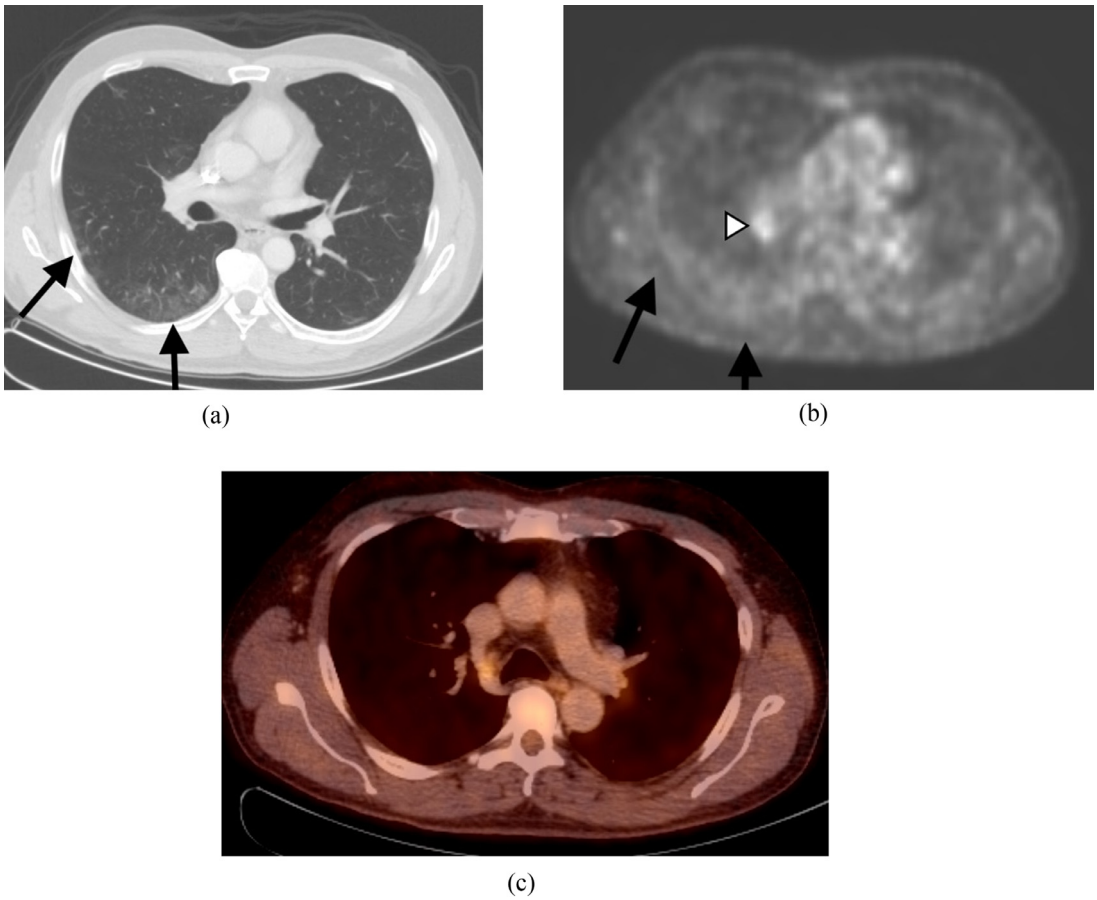

Figure 1 A 53-year-old male with a history of colorectal cancer presented for restaging FDG-PET/CT. Axial low dose CT image (A) showing incidental peripheral ground-glass opacity involving the posterior right lower lobe lung (arrows), with borderline hypermetabolism (SUVmax of 2.2) on corresponding CT attenuation corrected PET image (arrows in B). Additionally, mild uptake (SUVmax of 2.6) was seen in the right hilar region likely representing reactive lymphadenopathy (white arrowhead in B). Given the morphology of lung opacities, equivocal FDG uptake, and clinical suspicion, patient underwent RT-PCR testing and was confirmed to have COVID-19.

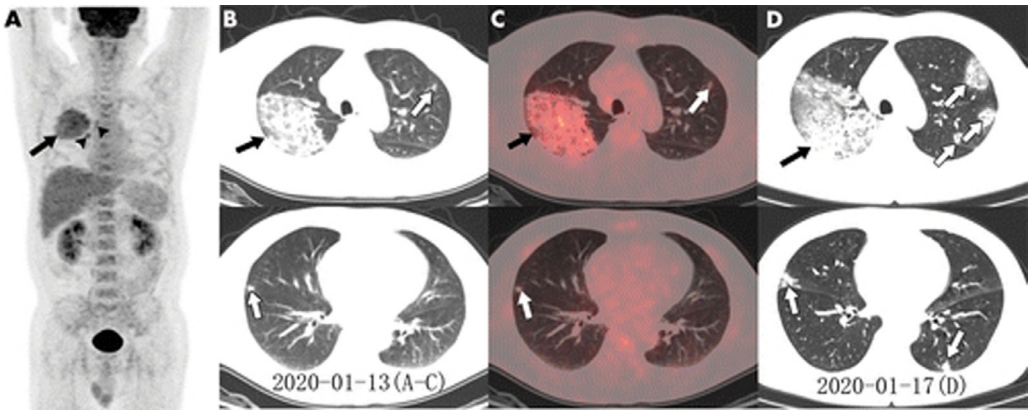

Figure 2 (A) PET maximum intensity projection image shows a fluorine 18 fluorodeoxyglucose (FDG)–avid mass (arrow) with a maximum standardized uptake value of 4.9 in the right lung. Increased accumulation of FDG in the right paratracheal, right hilar lymph nodes (arrowheads), and bone marrow are also noted. (B) Low-dose axial CT scan and, (C) PET/CT fusion image show ground-glass opacities with areas of focal consolidation (black arrow) primarily in the right upper lobe and a focal opacity in the left upper and right middle lobes (white arrows). (D) Follow-up CT scan obtained 4 days later demonstrates progression of lesions in bilateral upper and right middle lobes (arrows) with newly developed focal opacities in the left upper and lower lobes (arrows). Figure 2 reproduced with permission from Zou S, Zhu X. FDG PET/CT of COVID-19. Radiology 2020;296: E118-E118.

FDG-PET/CT should not be limited to the evaluation of oncologic conditions. With the growing evidence of the detection of COVID-19 on FDG-PET/CT studies, radiologists and nuclear medicine physicians should be aware of the features of SARS-CoV-2 infection on FDG-PET/CTs, as this may lead to the detection of crucial nononcologic pathologies. In patients with suspicious FDG-PET/CT findings for COVID-19, we recommend a low threshold for clinical/paraclinical screening and diagnostic testing such as PCR. This will allow earlier recognition, detection, and treatment of this potentially life-threatening and devastating disease, as patients undergoing FDG-PET/CT studies (usually for oncologic indications) are commonly immunocompromised and are more prone to severe disease or complications.[20] On the other hand, early recognition of suspicious patterns on FDG-PET/CT can help ensure optimal postexposure precautions and implementation of recommendations sooner.

FDG-PET/CT and Extrapulmonary Manifestations of COVID-19

COVID-19 is known to be associated with extrapulmonary involvement, such as renal dysfunction, hepatic, vascular, and myocardial injury, as well as neuromuscular and gastrointestinal abnormalities. Arterial and venous thrombosis has also been reported in hospitalized COVID-19 patients, particularly those who are severely ill. A US registry of 1114 COVID-19 patients reported that major arterial or venous thromboembolic complications 30 days from diagnosis occurred in 35.3% of 170 hospitalized intensive care unit (ICU) patients and only 2.6% of 229 hospitalized non-ICU patients.[21] Recent studies note a potential role of FDG-PET/CT imaging in detecting venous thrombosis throughout the body, as clots contain an abundance of activated white blood cells and platelets, which are highly glycolytic.[22-25] Progression of the disease from isolated pulmonary involvement to a systemic condition has a poor prognosis and can result in multiorgan failure[26-31] Thus, many authors have focused on the utilization of FDG-PET/CT for assessment of the extrapulmonary manifestations of COVID-19. Karimi-Galougahi et al[32] noted decreased metabolic activity in the orbitofrontal cortex associated with the COVID-19 induced anosmia (Fig. 3). In addition, these authors used FDG-PET/CT to investigate COVID-19 induced facial nerve palsy, and FDG-PET/CT findings have also indicated reduced neurological radiotracer uptake in several brain areas prior to symptom onset, during active illness, and 6 months after infection.[33-35] The acute reduction in uptake was primarily found in the prefrontal cortex, mimicking the patterns of several neurodegenerative disorders.[33-35] Other authors such as Sollini et al[36] have

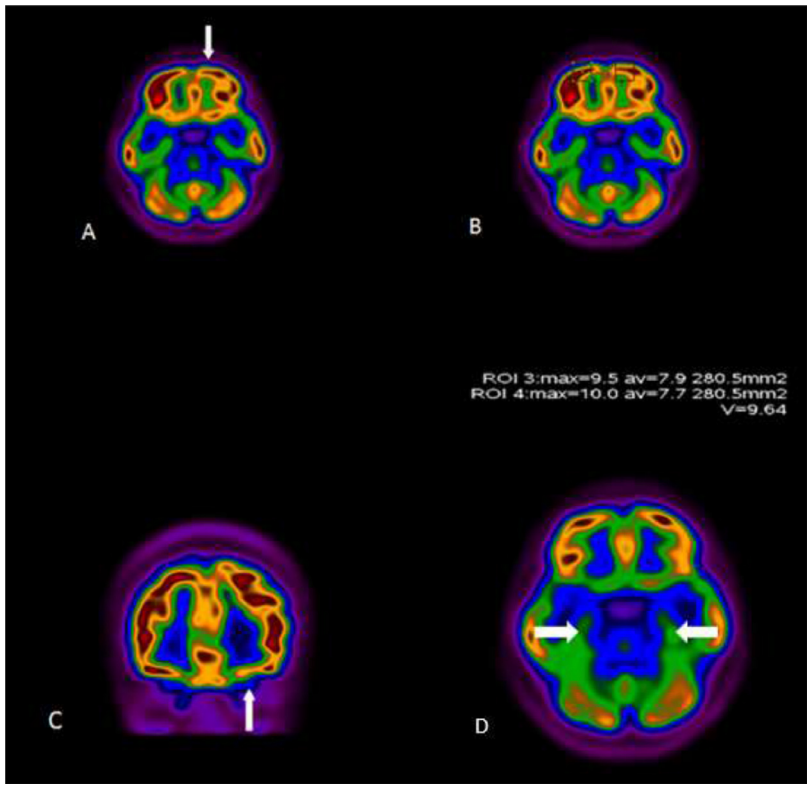

Figure 3 FDG-PET/CT scan of a 27-year-old woman with persistent anosmia and positive PCR for SARS-CoV-2. Representative axial (A, B, D) and coronal (C) images are shown. There was decreased uptake in the left orbitofrontal cortex (arrows). The uptake of temporal lobes were symmetric and normal (arrows, D). Figure 3 reproduced with permission from Karimi-Galougahi M, Yousefi-Koma A, Bakhshayeshkaram M, Raad N, Haseli S. 18FDG PET/CT scan reveals hypoactive orbitofrontal cortex in anosmia of COVID-19. Academic radiology 2020; 27:1042-1043.

identified increased FDG uptake in vasculature in those patients complaining of persistent symptoms postinfection. They found increased uptake in the thoracic aorta, right iliac artery, and femoral arteries, suggesting post COVID-19 vasculitis in symptomatic survivors.[36] Bai et al[11] found increased SUVmax in the liver of COVID-19 patients (4.31 ± 0.91 vs 2.86 ± 0.66, *P*= 0.017), indicating COVID-19 induced hepatocyte injury, although clinically significant liver injury was uncommon. Halsey et al[37] incidentally found increased gastrointestinal and renal uptake in asymptomatic COVID-19 patients with SUVmax values of 3.85 ± 1.12 and 4.03 ± 0.94 respectively. Though FDG-PET/CT has not been routinely utilized in presumed COVID-19 induced myocarditis, Puntmann et al[38] reported that cardiac MRI (CMR) is abnormal in 78% and ongoing myocardial inflammation in 60% of recently recovered COVID-19 patients at an average of 71 days postdiagnosis, suggesting significant residual disease burden. In this setting, FDG-PET/CT could have potential utility not only in diagnosis but also in differentiating between acute and chronic myocardial injury. Ultimately, further research is necessary to determine the added benefits of FDG-PET/CT imaging in assessing long-term extrapulmonary sequelae of COVID-19.

FDG-PET/CT and COVID-19 Vaccination

A routine FDG-PET/CT, because of its excellent sensitivity, may capture changes related to recent COVID-19 vaccination. Recent research has shown that reactive lymph nodal uptake on FDG-PET/CT may appear within a few days and persist for several weeks post COVID-19 vaccination.[39-41] For instance, Eshet et al[42] reported increased FDG uptake in the ipsilateral axillary lymph node with median SUVmax values of 2.9 ± 1.3, up to 10 weeks after vaccination. Avner et al[43] reported SUVmax values of up to 9.4 in the left axilla, retro pectoral space, and proximal arm 6 days after the second dose of Pfizer COVID-19 vaccine. These findings are not unexpected given previous evidence citing ipsilateral axillary node FDG uptake in influenza vaccine recipients.[44] However, it is imperative that interpreting physicians recognize this manifestation in oncologic patients to avoid unnecessary biopsy and restaging (Fig. 4).[39]

Respiratory Viral Infections

The most common causes of respiratory infection are viral pathogens, including influenza virus, human parainfluenza

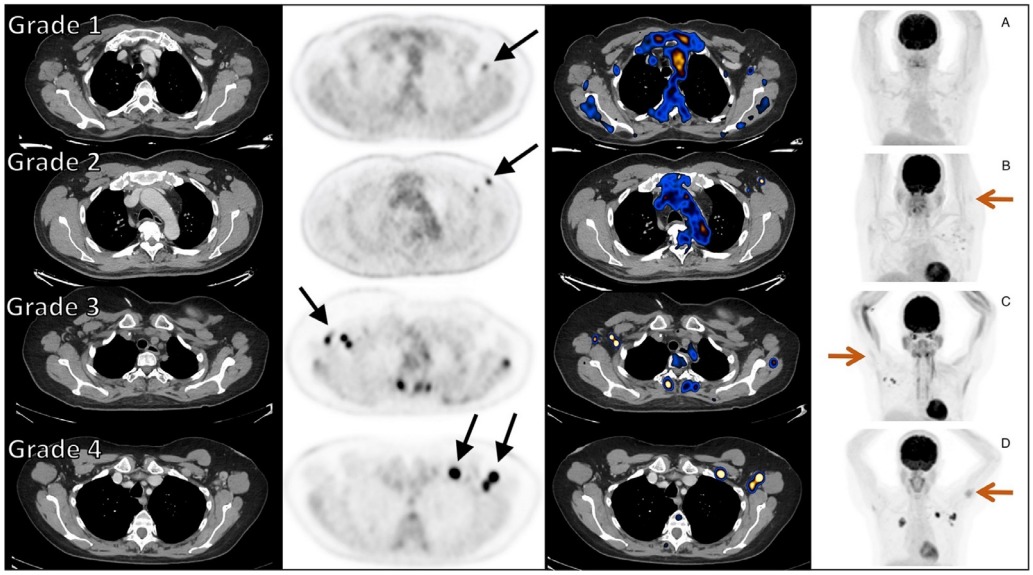

Figure 4 Grading of vaccine-associated hypermetabolic lymphadenopathy based on FDG-uptake intensity and nodal size: Grade 1, mild uptake intensity (SUVmax <2.2); Grade 2, moderate uptake intensity (2.2 ≤ SUVmax <4); Grade 3, high uptake intensity (SUVmax ≥4) in normal-size nodes; and grade 4, high FDG-uptake intensity (SUVmax ≥4) in enlarged nodes. Each row represents one patient. From left to right: CT, PET, and fusion PET-CT axial slices and a MIP image. HLN was identified in the axillary and supraclavicular lymph nodes (most likely due to recent vaccination, as annotated by black arrows) in each of the following patients: Patient A: colon cancer patient referred for staging imaged 9 days following the first vaccine dose (SUVmax of 1.97), Patient B: rectal cancer patient referred for follow-up, imaged 13 days following the second vaccine dose (SUVmax of 3.39), Patient C: prior history of breast cancer referred for follow-up study 10 days following the first vaccine dose (SUVmax of 10.10), and Patient D: right upper lobe lung cancer patient referred for staging 1 day following the booster vaccine dose (SUVmax of 14.34). Lymph node diameter of Patient D was noted to be 14 mm. Brown arrows indicate increased FDG uptake at the vaccine injection site on the MIP images. HLN, hypermetabolic lymphadenopathy; MIP, maximal intensity projection. Figure 4 adapted with permission from Cohen, D., Krauthammer, S. H., Wolf, I., & Even-Sapir, E. (2021). Hypermetabolic lymphadenopathy following administration of BNT162b2 mRNA Covid-19 vaccine: incidence assessed by (18)F-FDG PET-CT and relevance to study interpretation. Eur J Nucl Med Mol Imaging, 48(6), 1854-1863. https://doi.org/10.1007/s00259-021-05314-2. http://creativecommons.org/licenses/by/4.0/.

virus, rhinovirus, respiratory syncytial virus, and adenovirus. On top of that, there have been several regional and global outbreaks of novel respiratory viral infections during the past decades, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), H1N1 and H5N1 influenza, and most recently, COVID-19. CXR and CT are the routinely utilized imaging modalities to investigate pulmonary changes at presentation, as well as to monitor disease progression and response to treatment. The most common CT findings in viral respiratory illnesses include diffuse ill-defined GGOs, consolidation, and interlobular septal thickening.[45] These findings however are highly non-specific and can also be seen in some inflammatory diseases, as well as some nonviral infections.[46]

Acute inflammatory response has been shown to play an important role in the pathogenesis of severe respiratory dysfunction in respiratory viral infections such as H1N1, H5N1, and SARS.[47,48] During the acute inflammatory phase of infection, activated neutrophils heavily utilize anaerobic glycolysis, which leads to increased FDG uptake.[49] Hence, FDG-PET/CT has the potential to assess the degree of inflammatory response in respiratory viral infections.[47] This uptake can be quantified and may be very helpful in delineating the extent of inflammation in lung tissue. Furthermore, it has been shown that increased FDG uptake is present not only in nonaerated portions of the lungs on CT scan, but also areas with preserved aeration. This suggests improved sensitivity and more accurate estimation of inflammation utilizing FDG-PET/CT.[48] Tracking the underlying inflammation could potentially be useful in monitoring disease progression, response to treatment, and confirming resolution of infection.

Pulmonary Fungal Infections

Taking advantage of the quantifiable FDG uptake during the inflammatory response to infections, PET/CT has the potential to be utilized for initial diagnosis, staging of invasive fungal infections, disease progression, and response to treatment.[50-52] Semiquantitative FDG uptake has already been shown to be more accurate in measuring disease activity compared to morphological changes in lesion size visible on anatomic imaging.[53] Once the primary infection resolves, FDG-PET/CT can be useful in confirming inflammatory resolution in the setting of persistent structural abnormalities seen on other modalities.[53] Conversely, an increase in SUVmax has been shown to be associated with disease progression.[53] In addition to establishing diagnosis, FDG-PET/CT can also be useful in localizing occult fungal infections, particularly in immunocompromised patients (Fig. 5).[54]

Aspergillosis

Showing prominent FDG-avidity, pulmonary aspergillosis looks very similar to pulmonary malignancy on FDG-PET/CT, potentially creating confusion for the reading radiologist.[51,55] However, FDG-PET/CT can be effective in differentiating invasive and noninvasive pulmonary aspergillosis, given the higher peak SUV in the former.[14] Imaging manifestations of invasive aspergillosis are defined as multiple hypermetabolic nodules, while in noninvasive aspergillosis, solitary metabolic nodules with halo pattern have been described[14] FDG-PET/CT can also be utilized to investigate response to therapy in pulmonary aspergillosis, and has value in uncovering occult infection in the immunocompromised patient.[56]

Blastomycosis

Pulmonary blastomycosis can also mimic primary and metastatic lung malignancy on FDG-PET/CT, mostly due to high uptake in a nodular pattern.[57,58] Preclinical studies on animal models with blastomycosis showed FDG uptake levels higher than lymphoma.[59] A potential of FDG-PET/CT in pulmonary blastomycosis is the fact that it can show the true extent of active infection by discovering disease sites which are otherwise clinically occult.[59]

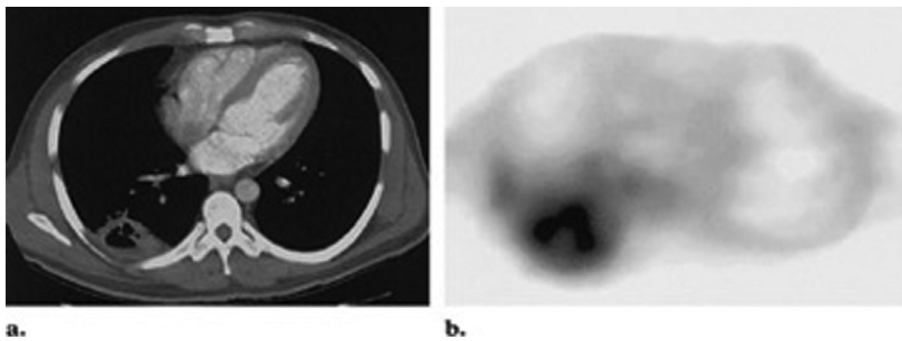

Figure 5 Fungal pneumonia in a 40-year-old man with AIDS and newly diagnosed anaplastic lymphoma. (A) Computed tomographic (CT) scan demonstrates a 6 × 3.5-cm thick- walled cavitary lesion in the posterior segment of the right lower lung. (B) FDG-PET scan demonstrates intense, heterogeneous accumulation of radiotracer in the posterior aspect of the right lower lung, a finding that corresponds to the abnormality identified at CT and that could indicate lymphomatous involvement of the pulmonary parenchyma. The final diagnosis, however, was fungal pneumonia. It was not possible to distinguish lymphoma from infection on the basis of the FDG-PET finding alone. Figure 5 reproduced with permission from Love, C., Tomas, M. B., Tronco, G. G., & Palestro, C. J. (2005). FDG PET of infection and inflammation. Radiographics, 25(5), 1357-1368. https://doi.org/10.1148/rg.255045122.

Candidiasis

Candidiasis lesions show increased FDG avidity on nuclear imaging, thus this modality could be utilized in guiding anticandida therapy.[60] In support of this, Xu et al[53] performed a preliminary study in patients with chronic disseminated candidiasis, and noted that FDG-PET/CT provided utility in antifungal therapy response. FDG-PET/CT can also help in the detection of occult sites of candidiasis in immunocompromised patients [50]

Coccidioidomycosis

Pulmonary coccidioidomycosis lesions have abnormal FDG uptake on PET/CT, but this modality is of limited use due to the difficulty differentiating these lesions from malignancy.[61] Nonetheless, the median SUVmax is often more elevated in malignant lesions relative to coccidioidal nodules with SUVmax of greater than 5.9 suspicious for malignancy.[62] Nia et al[63] reported a case of pulmonary coccidiomycosis with systemic involvement and discussed that FDG-PET/CT has the potential to guide medical management and help with investigating the extent of the disease, as well as response to therapy.

Cryptococcosis and Histoplasmosis

Pulmonary cryptococcus involvement can show variable levels of FDG avidity in PET/CT, ranging from mild to pronounced uptake.[64,65] The most common presentation is a solitary nodule, and less frequently: scattered nodular, clustered nodular, mass-like and bronchopneumonic patterns.[66] However, pulmonary cryptococcosis can show a similar pattern of FDG uptake to that of lung cancer.[67,68] Thus, cryptococcosis should be kept in the differential diagnosis when evaluating lung malignancy with FDG-PET/CT, especially in endemic areas. Thus far, multiple studies have indicated that FDG-PET/CT is unhelpful diagnostically, but may be useful when guiding response to treatment.[51] Pulmonary histoplasmosis also shows FDG avidity in PET/CT, both in the primary pulmonary infection and the mediastinal and hilar lymph nodes.[69] As with many other pulmonary fungal infections, nuclear imaging manifestations are similar to lung malignancy and create false positives, reducing the specificity of FDG-PET/CT in the detection of lung malignancies in endemic areas.[51,70] However, some authors have noted that dual-time FDG-PET/CT may be helpful in discriminating benign from malignant lesions.[71] In chronic histoplasmosis, Nagelschneider et al[72] have described a flip flop fungal sign on FDG-PET/CT that helps differentiate histoplasmosis from malignancy. Mittal et al[73] showed that FDG-PET/CT can be used in initial staging as well as in response to treatment. These authors have suggested the utility of FDG-PET/CT in the early identification of lesions amenable to therapy.

Mucormycosis

In a report, Dang et al[74] described their FDG-PET/CT findings in a case of pulmonary mucormycosis as prominent peripheral uptake in a heterogeneous soft tissue mass. Recent studies have also begun to recognize increased rhino-orbital mucormycosis susceptibility in patients with moderate to severe COVID-19 infection.[75]

Tuberculosis Infections

Tuberculosis (TB) infection of the lung primarily involves formation of a well-structured granuloma, in which immune cells and bacteria aggregate. In approximately 80% of cases, the lungs are the most common site of infection, but tuberculosis can disseminate to nearly any tissue or organ by hematogenous, lymphatic, or contiguous spread.[49]

FDG-PET/CT is a noninvasive tool capable of early detection and assessment of the disease involvement. This imaging modality is also capable of indicating enhanced glycolytic activity in both anaerobic and aerobic cells, thereby broadening its utility. This technique can demonstrate the disease extent, guide biopsy from active lesions, and find distant occult foci.[76] It can also measure treatment response to significantly optimize patient management.

As radiolabeled FDG accumulates in TB-related neutrophils, macrophages, and T-lymphocytes (all present in active granulomatous foci), this imaging method has high precision in identifying active granulomatous sites.[77,78] The ability of FDG-PET/CT to detect changes in metabolic uptake of TB lesions may be considered an accurate complementary tool to conventional anatomical imaging. A study by Stelzmueller et al[79] demonstrated that, while both FDG-PET/CT and CT scanning provide useful diagnostic information at both initial assessment and follow-up, FDG-PET/CT was more accurate and sensitive than CT scanning in the detection of suspicious pulmonary and extrapulmonary TB lesions. Other authors have reported that the addition of nuclear imaging to anatomic modalities such as CT further increased the sensitivity of this modality to identify small lesions, affected lymph nodes, and allowed differentiation between active and inactive lesions.[80,81]

Recent studies have also focused on the utilization of FDG-PET/CT for assessment of treatment effectiveness. Malherbe et al[82] concluded that quantitative metrics of FDG-PET/CT showing mean standardized lesion activity were predictive of treatment outcome. After one year of treatment, there was continuous dynamic reduction of lesions' activity demonstrated by FDG-PET/CT imaging.[82] Ultimately, FDG-PET/CT technique is of great value in determining TB progression, evaluating the efficacy of midterm treatment,[83,84] and in the detection of post-treatment disease recurrence.[85]

While FDG-PET/CT has shown to be effective in assessing metabolic activity of pulmonary lesions, some studies have indicated that FDG-PET/CT is more efficient than CT in assessing extrapulmonary involvement.[86] As 15% of TB patients present with extrapulmonary disease, it is imperative to identify the most sensitive diagnostic techniques, as imaging characteristics can often make M. tuberculosis lesions indistinguishable from tumors.[87] For example, Mao et al[87] have noted that the clinical and traditional imaging features of abdominal tuberculosis can mimic pancreatic cancer, and the location is often difficult to biopsy. In these circumstances, FDG-PET/CT imaging

combined with tuberculin testing or latent TB serology can help elucidate the correct diagnosis and help patients avoid unnecessary procedures.

Nontuberculous Mycobacterial Infections

In addition to TB infection, nontuberculous mycobacterial (NTM) infections can be detected using FDG-PET/CT. NTM infections are caused by a diverse and emerging group of pathogens and are rapidly increasing worldwide.[88] Mycobacterium avium complex (MAC) is the most frequently isolated atypical mycobacterium found in these cases. Similar to TB, the lung is the most common site of involvement leading to nonspecific clinical signs which could remain underdiagnosed.

As FDG collects in granulation tissues formed by activation of macrophages in NTM infection, the amount of FDG accumulation is positively associated with the scope of active inflammatory areas.[89] In a study by Del Giudice et al,[90] FDG-PET/CT was found useful in revealing the activity and extent of disease by monitoring metabolic activity of various pulmonary lesions in NTM disease. Another investigation by Demura et al[91] assessed the role of FDG-PET/CT in the diagnosis and treatment monitoring of NTM infection. They confirmed that after one or two years of therapy for MAC, the FDG uptake associated with disease decreased, in spite of the persistence of lesions on CT scanning.[91]

Another significant feature of FDG-PET/CT imaging is the potential capability in evaluating disease progression and follow-up in NTM patients. Namkoong et al,[92] described an HIV and MAC-infected patient whose FDG-PET/CT findings identified disease progression on follow-up. In addition, this imaging technique was useful for assessing the required duration of anti-mycobacterial therapy. Accordingly, FDG-PET/CT could play a valuable role in patient management, particularly in complicated cases such as HIV, in which TB and NTM infections often result in disseminated disease and tend to relapse even after treatments.

Summary

Pulmonary infectious diseases are a major cause of morbidity and mortality worldwide, thus the utilization of FDG-PET/CT in conjunction with conventional imaging techniques can yield early diagnosis and optimize treatment strategies. Throughout this paper, we have highlighted the added clinical value of FDG-PET/CT for diagnosis, elucidating acute pulmonary/extra-pulmonary manifestations, and tracking treatment effectiveness. FDG-PET/CT imaging allows for a highly sensitive approach to imaging; thus, it has utility in recognizing disease early and guiding medical management. While usually not a first line imaging modality, FDG-PET/CT can be a useful adjunct to traditional imaging techniques to help reduce disease burden and provide vital information at the molecular level. In addition, FDG-PET/CT imaging is in alignment with medicine's shift to a more patient oriented approach.[93] Nuclear imaging has the advantage of allowing histological mapping and a personalized method of treatment, but further research is necessary to fully explore and validate the effectiveness of FDG-PET/CT imaging as a stand-alone modality in the setting of infectious diseases.

Author Contributions

LSE, BR and SA drafted the manuscript with support from AG and AA. AG developed the theory, provided feedback and guidance. All authors reviewed the manuscripts and provided edits prior to submission. LSE finalized the manuscript. LSE and BR contributed equally to the work and should be considered as co-first authors.

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