Heterogeneous imaging features of Aspergillosis at $^{18}$F-FDG PET/CT

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Abstract

Aspergillosis is one of the most frequent fungal infections, whose morbidity can be life-threatening, especially in some categories of patients such as immunocompromised ones. It can have various clinical presentation scenarios and should be considered when making differential diagnosis in patients with pulmonary and extrapulmonary involvement. $^{18}$F-FDG PET/CT is a whole-body diagnostic technique that can help in the study of the disease, guiding the patient management thanks to the possibility to recognize infection sites and extension. The aim of this manuscript is to provide an overview of the wide spectrum of disease presentation. Literature regarding $^{18}$F-FDG PET/CT in histologically confirmed aspergillosis cases has been revised to describe all its possible features, both usual and unusual to guide imaging interpretation. $^{18}$F-FDG PET/CT is a diagnostic tool that can help in the recognition of the heterogenous infection’s presentation, allowing the clinicians to make a prompt diagnosis and to have the most accurate management of the disease. Furthermore, other PET/CT radiopharmaceutical role in Aspergillosis imaging study have been presented.

Keywords  Nuclear medicine · $^{18}$F-FDG PET/CT · Aspergillosis · *Aspergillus fumigatus* · Fungal infections

Introduction

Fungal infections are very common diseases with several possible clinical manifestation, varying from local forms to multiorgan impairment. Their diagnosis is based on clinical signs and subsequent histopathological confirmation, and they are easily curable in most cases [1].

Nevertheless, these infections can be burdened by high rates of morbidity and mortality when occurring in immunocompromised patients. The prevalence of invasive fungal infections has been increasing in the last decades, with frequent life-threatening disseminated involvement [2].

Treatment timing is crucial and specific therapies should be introduced, even if frequently accompanied by side-effects, avoiding inadequate treatment strategies that could lead to disease progression [3].

The evaluation of disease extent and treatment efficacy is fundamental and generally assessed by traditional imaging techniques, according to anatomical changes, that unfortunately may persist for a long time even after the pathogen has been eliminated. Conversely, metabolic changes are prior to anatomical ones and can be detected by radionuclide-based techniques [4].

In this challenging scenario, nuclear medicine imaging is gaining relevance and the performance of the $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) for infectious diseases’ evaluation is increasing [5–7]. $^{18}$F-FDG PET/CT can detect metabolic treatment response guiding therapeutic choices during patients’ management [8].

The aim of our work is to describe all possible features of aspergillosis at $^{18}$F-FDG PET/CT and the state of art about its role in the management of this disease.

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Aspergillosis: epidemiology, clinical presentation, and diagnosis

Aspergillosis is a widespread fungal infection caused by inhalation of spores (conidia) of the ubiquitous mold *Aspergillus* [9, 10]. Among over 1.5 million environmental fungal species, more than 200 species of *Aspergillus* have been described, with only a percentage of them (10%) pathogens to humans [11]. The most frequent causative agent is *A. fumigatus*, followed by *A. flavus* and *A. niger*, and the most common frequent sites of localization are superior airways and lungs [12].

When pathogen infection occurs, the interaction between the host’s recognition cells and the fungi’s spores induces the inflammatory response with subsequent migration of white blood cells and phagocytosis of the fungi [13]. In immune-competent people, this process is valid and generally leads to the elimination of the pathogen. Conversely, when the host is immunodeficient, the response can be insufficient, and the infection progresses: conidia can germinate and invade the bloodstream with hyphae, to the point of endangering the patient’s life [4].

One of the limiting factors of spores’ development and subsequent infection progression in the host is the availability of iron, that is not directly accessible for the fungi in human blood. To evade this nutritional immunity system, *Aspergillus* can produce some molecules, called siderophores, with high affinity for ferric ions, guaranteeing itself the iron supply [1].

The predisposing causes of an inefficient metabolic host response are numerous, the most frequent being genetic characteristics, oncological conditions, HIV infection, prolonged and/or concomitant chemotherapies or immunosuppressive drug treatments, post-transplant conditions, lung comorbidities and other chronic diseases (e.g., chronic kidney failure, long-standing diabetes mellitus, alcoholism, chronic liver disease, malnutrition) [14].

The clinical presentation of Aspergillosis is variable, ranging from local airways infection to systemic dissemination (Table 1). The sites most frequently involved by distant hematogenous dissemination are central nervous system, heart, kidney, and liver [15, 16].

The potential lethality of *Aspergillus* makes it a significant burden to immunocompromised patients in clinical experience. Its early detection is challenging and can lead to delayed treatments, impacting on patient survival [9].

Temporistic diagnosis of aspergillosis is generally problematic because of its clinical non-specific signs, such as fever, cough, chest pain, shortness of breath and headache, that mimic many other lung disease conditions [17].

The gold standard for the diagnosis of Aspergillosis is fungal culture from sterile biopsy, as diagnostic completion to other biomarker exams. Unfortunately, the sensitivities of this tests are poor and can be influenced by empiric antifungal treatments previously established [9].

Traditional instrumental imaging is usually performed to allow a diagnostic-driven approach, but radiological findings of Aspergillosis are non-specific, and the CT finding called “halo-sign” is transient and only suggestive but non-pathognomonic of *Aspergillus* infection [18].

In the last years, additional laboratory methods, such as bioluminescence, and nuclear medicine imaging techniques have been developed, to overcome the limitation of the challenging detection of *Aspergillus* infection [19].

| Table 1 | Clinical manifestation and predisposing conditions of the most frequent *Aspergillus*-related airway diseases |
| Aspergillus-related airway diseases | Predisposing conditions |
|-----------------------------------|------------------------|
| Superior airways infection (rhinosinusitis, tracheo-bronchitis) | Transitory reduced immune host response |
| Saprophytic aspergilloma | Pre-existing lung cavities from tuberculosis, fibrobullos sarcoidosis or bronchiectasis |
| Allergic broncho-pulmonary aspergillosis (ABPA) | Previous sensibilization or cystic fibrosis |
| Chronic pulmonary aspergillosis (CPA) | Impaired immune state due to chronic obstructive pulmonary disease, previous pulmonary tuberculosis, thoracic surgery, radiation therapy, pneumoconiosis, cystic fibrosis, lung infarction, sarcoidosis, low-dose corticosteroid therapy or other chronic diseases |
| Invasive pulmonary aspergillosis (IPA) | Immunodeficiency due to prolonged neutropenia, hematopoietic stem cell and solid organ transplantation, high-dose prolonged corticosteroid therapy, hematological malignancy, cytotoxic therapy, AIDS, and chronic granulomatous disease |
**18F-FDG PET/CT: rational use and advantages**

18F-FDG PET/CT is a nuclear medicine technique whose role is predominant in the oncological field, and, over recent years, is gaining importance also in the diagnosis and monitoring of infectious diseases [20–22].

The advantages of 18F-FDG PET/CT are numerous and can influence every phase of the management of patients with *Aspergillus* infection, from the initial diagnosis to the treatment strategy planning [2, 23].

18F-FDG is a glucose analogue taken up by cells via a membrane transporter (GLUT-1 and GLUT-3) and trapped into them after phosphorylation; therefore, its intracellular concentration is proportional to cell’s metabolism. Cellular glucose utilization typically increases in activated leucocytes during infection and inflammations, resulting in an intense 18F-FDG uptake, detectable by PET/CT [8]. According to this, 18F-FDG PET/CT is a useful tool when clinical suspicion of Aspergillosis is formulated, in particular in the early phases of the fungal infection when anatomical changes are not detectable by other imaging methods yet [24].

Furthermore, 18F-FDG PET/CT scan accounts a whole-body acquisition, that allows to have an overview of all the districts possibly involved by the disease. This aspect is fundamental especially in cases of suspicion of disseminated and systemic Aspergillosis, that easily occurs in debilitated patients whose compliance to undergo numerous and prolonged imaging exams is low. The possibility to acquire detailed information of all the body is of great importance for a more comprehensive assessment of the patient’s global disease [22, 25].

Besides diagnosis facilitation, 18F-FDG PET/CT can be useful as a guide for targeted biopsy. When widespread disease is suspected, 18F-FDG PET/CT can reveal many hypermetabolic lesions and help in detecting the most easily attackable for surgical biopsy. If percutaneous operations are performed before metabolic imaging, they can result inconclusive in case normal parenchyma is biopsied, delaying the diagnosis and prolonging inadequate antifungal drugs, with a negative prognostic impact on patient’s survival [26].

The greater advantage offered by 18F-FDG PET/CT is that it can influence the therapeutic management of Aspergillosis. The comparison between baseline 18F-FDG PET/CT at diagnosis and 18F-FDG PET/CT after antifungal treatment is of utmost significance because it can guide the therapeutic strategy: it can confirm the utility of the current therapy or, on the other hand, show its inefficacy, suggesting stopping or switching it [5]. This aspect has been shown to have an influential prognostic value by influencing decision-making and choosing the most efficacy treatment. As metabolic changes occur earlier than the anatomical ones induced by *Aspergillus*, functional imaging demonstrates its importance because it can monitor the metabolic indices associated to fungal infection [3].

**Aspergillus: 18F-FDG PET imaging presentation, unusual localizations, and mimicking conditions**

The variability of Aspergillosis clinical manifestation reflects in a wide range of possible 18F-FDG PET imaging presentations. A correct image interpretation is necessary, with intensity of 18F-FDG accumulation sites and their pattern distribution being the most important elements to be considered as guide for PET images’ analysis. All clinical conditions possibly mimicking the infection should be considered when making differential diagnosis [27].

18F-FDG PET/CT is usually performed following standard protocols as regards both patient preparation and acquisition procedure, according to EANM guidelines. The acquisition is carried out cranial-caudally from the external acoustic meatus to the root of the thigh, with patient in a supine position and arms raised above his head [28].

When evaluating patients affected by Aspergillosis, it should be considered that infection spread can be systemic thus supplementary district acquisitions could be required in addition to the standard whole-body study. Head evaluation can detect possible brain involvement as well as limbs visualization can identify distant tissues commitment, such as during arthritis and myositis due to infectious involvement. Personalized acquisition protocols are preferred and should be established after a complete assessment of each patient’s clinical situation [8].

Images evaluation has to be performed both qualitatively and quantitatively. About qualitative analysis, increased 18F-FDG uptake sites are visually detected and adequately described considering: pattern distribution (focal, linear and/or diffused), homogeneity and intensity. As regards quantitative analysis, the most frequent parameter used is maximum standardized uptake value (SUV\textsubscript{max}); nevertheless, there is not a univocal consensus about its superiority to other parameters yet. Other indices have been considered suitable for disease assessment, such as mean standardized uptake value (SUV\textsubscript{mean}), peak standardized uptake value (SUV\textsubscript{peak}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV and TLG seem to be more representative than others because they evaluate the glucose uptake from all lesions. At current state, systematic studies comparing different parameters’ reliability have not been conducted so no real agreement which is the best index is statable yet [3].
Imaging presentation of lung localizations

Single Aspergillosis localization is frequent in lung parenchyma when saprophytic aspergilloma occurs. Sharma et al. described an exemplary case of non-invasive aspergillosis detected by $^{18}$F-FDG PET/CT as solitary pulmonary nodule showing mild glucose uptake, with peri-nodular opacity, called “halo sign”. When mild $^{18}$F-FDG uptake is detectable, in concomitance with single pulmonary lesions visible on CT co-registered images, inactive fungal infection can be suggested, excluding non-invasive Aspergillosis. Differential diagnosis with lung neoplasm should be evaluated, considering glucose uptake intensity and clinical-laboratory examinations [8].

An example of isometabolic nodule is the one described by Ahn et al. in a patient with suspected pulmonary metastasis from thyroid cancer, whose $^{18}$F-FDG PET/CT images showed a single nodule with slight glucose uptake; histologic confirmation subsequently confirmed the diagnosis of pulmonary aspergilloma [29].

Single pulmonary localization is not necessarily detected by mild and homogeneous glucose uptake, but can have other imaging appearances, as depicted by Kim et al. The lesion can show as one of the following types of evidence: isometabolic halo pattern, defined as a central cold area and a surrounding mildly increased metabolism sign; isometabolic nodule pattern, when the lesion has a glucose uptake similar to or less than the mediastinal blood pool; hypermetabolic nodule pattern, when the lesion has a glucose uptake higher than the mediastinal blood pool [30].

Single pulmonary nodule characterization by $^{18}$F-FDG PET/CT is challenging and not universally defined yet, as a definite diagnosis can be guaranteed only by histopathological confirmation.

In Figs. 1, 2, 3, we described exemplary cases of single pulmonary Aspergillosis localization at $^{18}$F-FDG PET/CT that differ for $^{18}$F-FDG uptake pattern, from slight and non-homogeneous to focal and intense. All patients described had immune system impairment and definite

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**Fig. 1** $^{18}$F-FDG PET/CT images of a patient who developed pulmonary Aspergillosis after a long-time immunosuppressing therapy for treatment of autoimmune disease. Axial (a, b), coronal (c, d) and sagittal (e, f) PET and fused images showed slight and non-homogeneous $^{18}$F-FDG uptake in a lesion sited in the upper right lobe ($\text{SUV}_{\text{max}}$ 2.6) (green arrows)
diagnosis was performed by *Aspergillus* identification in fungal culture (Figs. 1, 2, 3).

Imaging detection of allergic broncho-pulmonary aspergillosis (ABPA) can reveal a major glucose-avid pulmonary mass accompanied by multiple $^{18}$F-FDG up taking lymph nodes. Baxter et al. described the case of a patient with clinical suspicion of Aspergillosis who underwent $^{18}$F-FDG PET/CT staging, that resulted diriment. Nuclear medicine imaging showed a single lung lesion abutting the pleura with intense $^{18}$F-FDG uptake associated with numerous lymph nodal masses and guided the biopsy, leading to a definite diagnosis and an adequate treatment strategy [27].

Aspergillosis becomes threatening for patients’ health when evolving in chronic and invasive disease forms, frequently occurring in people with previous predisposing diseases and/or concomitant immunosuppressive drug treatments.

Chronic pulmonary aspergillosis (CPA) can be commonly detected in patients with pre-existing cavitating lesions, as depicted in various clinical cases described in the literature. $^{18}$F-FDG PET/CT imaging can notice high glucose uptake in the cavitation, that can also be extended to the contiguous pleura, with a surrounding intermediate uptake, attributable to peripheral fibrosis. Other pulmonary diseases with similar radiological features should be excluded in the diagnostic evaluation, in particular in patients with positive clinical history for previous comorbidities, such as tuberculosis [27].

A case of invasive pulmonary Aspergillosis is reported in Fig. 4; a patient developed Aspergillosis because of the presence of previous cavitary lesions due to tuberculosis, a frequent predisposing factor. $^{18}$F-FDG PET/CT images showed peri-nodular tracer accumulation in the left pulmonary apex, around the cavitary lesion and close to the adjacent pleura, that appeared involved in the infectious process. The $^{18}$F-FDG PET/CT examination was particularly useful in the assessment of this patient because it allowed the detection of an unsuspected skeletal localization at the 9th right rib, not visible on the low dose CT co-registered images, demonstrating and supporting the evidence that anatomical
changes may not be detectable by other imaging methods in the initial stages of the disease (Fig. 4).

A rare but potentially aggressive variant of Aspergillosis is subacute invasive pulmonary Aspergillosis (sIPA), formerly called chronic necrotizing pulmonary aspergillosis (CNPA). Its progression is more rapid than the chronic forms and its diagnosis is challenging as it can mimic neoplasms. Both single and multiple lesions can be detected as large, centrally necrotic, markedly glucose-avid lesions, potentially suspected of lung primitive or secondary localization. $^{18}$F-FDG uptake can involve the adjacent pleura as well as lymph nodes [31–33].

Invasive pulmonary aspergillosis (IPA) has poor prognosis and a high mortality rate in immunocompromised patients, making its timely diagnosis of primary importance. $^{18}$F-FDG PET/CT detection of lesions’ metabolic activity can be suggestable of infection’s future behavior [8, 30]. In a study conducted by Bryant et al. concerning pulmonary nodules, glucose avidity of fungal infections was found to be the highest among benign lesions (median $S_{\text{UVMAX}}$ 7.2) and very close to the value of adenocarcinomas (median $S_{\text{UMAX}}$ 9.4), reflecting their intense metabolic activity [34]. Lee et al. depicted a case of invasive tracheobronchial aspergillosis, a form of IPA confined to tracheobronchial tree, in a patient previously treated with chemotherapy and radiotherapy for lung carcinoma. After a free-disease survival period, the patient showed persistent cough and dyspnea and underwent CT for the suspicion of cancer recurrence and radiation mediastinitis. Successively $^{18}$F-FDG PET/CT was performed, and a moderate glucose uptake was detected in an abnormal soft tissue mass surrounding the trachea and the mediastinum, extending to the main bronchi. Fibrosing mediastinitis was suspected but the subsequent $^{18}$F-FDG PET/CT guided biopsy confirmed the infectious disease [35].

Considering the ability to characterize lesions’ FDG avidity, $^{18}$F-FDG PET/CT is a significant tool in monitoring the efficacy of antifungal therapy. By comparing the semiquantitative values obtained by two or more consecutive $^{18}$F-FDG PET/CT scans, metabolic changes can be valuable and
predictable of treatments response. Kim et al. described the representative case of a patient with IPA following chemotherapy for hematological disease. Initial 18F-FDG PET/CT images showed multifocal hypermetabolic nodules and consolidative lesions in both lungs; after adequate antifungal treatment, 1-month follow-up 18F-FDG PET/CT images, compared to staging imaging, showed a significant decrease in size and metabolic activity of detected lesions [30].

Usual and unusual imaging detection of extra-pulmonary localizations

Manifestation of extra pulmonary localization of Aspergillosis are conceivable when patient’s immune response is highly compromised. Hematogenous spread allows the infection to extent in every district, with central nervous system, liver, spleen, kidneys, muscular-skeletal system being the more frequently involved. 18F-FDG PET/CT can show intense metabolism revealing lesions not demonstrated on the traditional radiological images [26].

Gruter et al. depicted the case of a woman with unexpected invasive Aspergillosis of the central nervous system. The patient performed 18F-FDG PET/CT to search the occult malignancy responsible of suspected secondary lesions detected in brain by traditional CT and MRI. Nuclear imaging showed the presence of hypermetabolic tissue both in the lung parenchyma and in the adrenal gland and the subsequent histology confirmed the infectious nature isolating Aspergillus. 18F-FDG PET/CT execution was central in the disease assessment of the patient, being able to recognize adrenal involvement otherwise unsuspected, in addition to the pulmonary one. The whole-body acquisition allowed a complete evaluation of the systemic commitment, guiding the antifungal treatment and leading to the clinical resolution of the disease [36].

A similar clinical case of a patient affected by invasive Aspergillosis with systemic localizations is reported in Fig. 5. The patient had a previous diagnosis of adenocarcinoma of the upper half of the left lung, treated with chemotherapy and radiotherapy, followed by monoclonal antibodies therapy; thus, the immune system impairment facilitated the subsequent fungal infection development and spread. 18F-FDG PET/CT detected an expected mild and diffuse tracer uptake in both lungs, but other glucose uptake sites were identified in regional adenopathies, skeletal localizations and multiple brain lesions (Fig. 5).

The dissemination to liver and spleen parenchyma can frequently be found in patients with highly compromised immune system. It is usually accompanied by the involvement of other organs, underlying the potential lethality of the invasive fungal infection. As well as other authors previously, Hod et al. demonstrated the massive hepatic and splenic commitment in a patient with hematological disease whose 18F-FDG PET/CT images showed numerous multifocal lesions with intensely increased uptake. Many of the liver hypermetabolic sites were unrecognizable on
CT components of the study, indicating the potentiality of the nuclear imaging study in the early recognition of the disease behavior. The whole-body examination allowed to detect another unsuspected infectious localization, unapparent on the CT component of the study too: an intramuscular lesion was demonstrated to be in one leg [25, 26].

Kidney is an unusual Aspergillosis localization: renal involvement by Aspergillus is rare, generally occurring in patients with predisposing conditions, and its differential diagnosis should include various primary and secondary renal neoplasms as well as other nephrological disorders (e.g., pyelonephritis, abscesses, granulomatosis diseases and infarctions). A peculiar case of renal aspergilloma in which 18F-FDG PET/CT demonstrated its additional value to diagnostic-therapeutic patient’s management has been described by Bulakci et al. A patient underwent a follow-up 18F-FDG PET/CT for hematological malignancy and an unexpected glucose uptake was revealed in lungs and in a kidney lesion. CT findings were compared to nuclear images and 18F-FDG pattern uptake was suggestive of infection: the lesion had a peripheral glucose uptake surrounding a central hypometabolic zone. Pulmonary fine needle aspiration and renal biopsy were performed, and confirmation of Aspergillosis was obtained. The diagnosis led to a change in clinical patient’s management and surgical removal of kidney was executed [37].

The muscle-skeletal system is uncommonly involved by Aspergillosis; nevertheless, pan-costochondritis and skeletal localizations have been recently described. Olivan-Sasot portrayed the case of a patient with thoracic pain who underwent 18F-FDG PET/CT whose images showed an important and diffuse uptake of the radiopharmaceutical in the stern and in the costal cartilages bilaterally, not just in the joints. No alterations were detected on the CT component, but metabolic changes detected by nuclear imaging were suspected and biopsy was performed. The diagnosis of pan-costochondritis due to Aspergillus was confirmed and 18F-FDG PET/CT was considered of outmost importance because it provided an early diagnosis and treatment, avoiding unnecessary further examinations [38]. Similarly, the case described by Landaburu et al. demonstrated the usefulness of 18F-FDG PET/CT performed in a patient with chest pain and unsuspected Aspergillus rib localization. Nuclear imaging identified an intense focal glucose uptake in the rib cage and the adjacent soft tissues, when CT images were inconclusive for a definite diagnosis of suspected neoplasm [39]. Kawabe et al. portrayed one of the first cases of aspergillosis of the paranasal sinus investigated by nuclear medicine imaging of a patient with a 2-month history of progressive left nasal obstruction and left rhinorrhea. 18F-FDG PET/CT scan detected an annular-shaped glucose uptake in the periphery of the left maxillary sinus, with a relatively higher 18F-FDG uptake extending from the interior of the sinus to the nasal cavity. Although the intensity of glucose uptake was not diriment to differentiate between benign and malignant lesions, 18F-FDG PET/CT images were used as a guide for biopsy and histological confirmation of Aspergillus localization was obtained [40].

Besides in immunocompromised adult patients, some rare cases of invasive Aspergillosis in critically ill pediatric population have been depicted in the literature [41, 42]. A peculiar case of disseminated Aspergillosis in a young patient
affected by flu was described by Mendoza-Palomar et al. “Influenza associated pulmonary Aspergillosis” (IAPA) involved multiple organs of the little patient, with high uptake lesions in fungal localizations in paranasal sinuses, eyes, lungs, spleen, bone, and soft tissues. 18F-FDG PET/CT was performed periodically to monitor the metabolic evolution of the lesions: it showed persistent high activity foci during antifungal treatment, demonstrating its inadequacy, and the following resolution of infection with reduction of glucose uptake, after therapeutic splenectomy. Thus 18F-FDG PET/CT provided information that influenced the therapeutic decision for the disease assessment and patient management [43].

Finally, a study by Wu et al. demonstrated that cases of Aspergillosis could possibly happen in immunocompetent patients. It is an exceptional eventuality, but systemic fungal infection should be supposed when the clinical suspicion is high. 18F-FDG PET/CT is a useful tool to be considered to distinguish active lesions by inactive ones [15].

**Other PET/CT tracers and future perspectives**

Besides established 18F-FDG, other PET tracers have been proposed in Aspergillosis evaluation.

Exploiting the fungi production of iron-avid siderophores, the latest can be labelled with analogues of iron such as Gallium 68 (68Ga) and Zirconium 89 (89Zr) to easily detect the active fungi with high specificity [1, 44, 45].

Studies about immuno-PET application in infectious diseases are few. As regards Aspergillosis a specific monoclonal antibody JF5 has been developed: it can bind the extracellular antigens produced by the fungi detecting the infections and, as it is produced only during active hyphae’s growth, JF5 can accurately discriminate inactive spores from growing invasive hyphae. As siderophores, monoclonal antibody JF5 can be labeled with 64Cu and 89Zr [4, 9, 46].

In in vitro studies antifungal agents have been labelled with PET tracers, such as fluconazole and amphotericin with 68Ga, to help the detection of drugs accumulation in infectious sites [4, 47].

The above-mentioned PET/CT tracers have not been used in humans yet, so their utilization is promising, but still under evaluation.

Labelling white blood cells with 64Cu or other radioisotopes has been proposed considering the advantage to delayed images acquisition, but the need to handle blood products make this procedure difficulty practicable [4].

Lastly, antimicrobial peptides have been labelled to 86Ga, but their unstable structure influence their ability to target fungi in a sensitive way [4].

In addition to PET/CT devices, PET/MRI tomographs utilization is beginning to spread in the nuclear medicine field; MRI can be considered as complementary radiological examination to PET images, when using antibody-guided radioisotopes, obtaining a significant reduction of dose exposition and improving image resolution [9, 48].

**Conclusions**

The present work resumes the most important features of Aspergillosis, underlying its variability in clinical presentation. It is a disease that should be considered when making differential diagnosis in patients with pulmonary and extrapulmonary involvement. Imaging appearance of fungal-induced lesions is extremely various and in this overview we resume and describe both usual and unusual fungal infection imaging manifestations detectable by 18F-FDG PET/CT. Clinicians should consider 18F-FDG PET/CT in the diagnostic-therapeutic management of patients with suspicion of Aspergillus infection, to define a complete assessment and establish the most suitable therapy.

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**References**

1. Pfister J, Summer D, Petrik M et al (2020) Hybrid imaging of Aspergillus fumigatus pulmonary infection with fluorescent, 68ga-labelled siderophores. Biomolecules. https://doi.org/10.3390/biom10020168
PET/CT. Clin Nucl Med 43:e381–e382. https://doi.org/10.1097/RLU.0000000000002237

39. Landaburu MF, López Daneri G, Ploszaj F et al (2019) Osteomyelitis of the rib cage by Aspergillus flavus. Revista Iberoamericana de Micología 36:86–89. https://doi.org/10.1016/j.riam.2019.02.002

40. Kawabe J, Okamura T, Koyama K et al (1998) Relatively high F-18 fluorodeoxyglucose uptake in paranasal sinus aspergillosis: a PET study. Case Rep Ann Nucl Med 12:145–148. https://doi.org/10.1007/BF03164779

41. Ankrah AO, Sathekge MM, Dierckx RAJO, Glaudemans AWJM (2016) Imaging fungal infections in children. Clin Transl Imaging 4:57–72. https://doi.org/10.1007/s40336-015-0159-2

42. Theobald I, Fischbach R, Hülskamp G et al (2002) Pulmonary aspergillosis as initial manifestation of septic granulomatosis (chronic granulomatous disease, CGD) in a premature monozygotic female twin and FDG-PET diagnosis of spread of the disease. Radiologe 42:42–45. https://doi.org/10.1007/s117-2002-8116-0

43. Mendoza-Palomar N, Melendo-Pérez S, Balcells J et al (2021) Influenza-associated disseminated aspergillosis in a 9-year-old girl requiring ECMO support. J Fungi. https://doi.org/10.3390/jof7090726

44. Petrlik M, Vlckova A, Novy Z et al (2015) Selected 68Ga-sidrophores versus 68Ga-colloid and 68Ga-citrate: biodistribution and small animal imaging in mice. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 159:60–66. https://doi.org/10.5507/bp.2014.052

45. Luptáková D, Pluháček T, Petřík M et al (2017) Non-invasive and invasive diagnoses of aspergillosis in a rat model by mass spectrometry. Sci Rep. https://doi.org/10.1038/s41598-017-16648-z

46. Thornton CR (2008) Development of an immunochromatographic lateral-flow device for rapid serodiagnosis of invasive aspergillosis. Clin Vaccine Immunol 15:1095–1105. https://doi.org/10.1128/CVI.00068-08

47. Page L, Ullmann AJ, Schadt F et al (2020) In vitro evaluation of radiolabeled amphotericin B for molecular imaging of mold infections. Antimicrob Agents Chemother. https://doi.org/10.1128/AAC.02377-19

48. Rolle AM, Hasenberg M, Thornton CR et al (2016) ImmunoPET/MR imaging allows specific detection of Aspergillus fumigatus lung infection in vivo. Proc Natl Acad Sci U S A 113:E1026–E1033. https://doi.org/10.1073/pnas.1518836113

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