

# <sup>18</sup>F-FDG PET/CT contribution to diagnosis and treatment response of rhino-orbital-cerebral mucormycosis

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## Abstract

**Objective:** Mucormycosis is an infection caused by mycetes mucorales, emerged as a life-threatening infection associated with severe morbidity and high mortality. Conventional imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) are usually performed to assess mucormycosis extension, but they may present insufficiencies in their performance. **Case presentation:** We present the case of a 13 years old patient with diagnosis of rhino-orbital-cerebral mucormycosis (RCM) who performed head MRI and [<sup>18</sup>F]2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) both for the infection spread assessment and for the early evaluation of response to systemic amphotericin-B treatment. **Conclusion:** This case suggests that <sup>18</sup>F-FDG PET/CT could be considered as a valuable tool for the initial staging of RCM when compared with MRI and should be performed as soon as possible after the first clinical suspicion of this disease. In addition <sup>18</sup>F-FDG PET/CT may also be useful for the assessment of response to treatment.

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## Introduction

Mucormycosis is an infection caused by mycetes of the order Mucorales. These organisms are normally found in dust, soil and also in upper respiratory mucosa of healthy individuals. They may become pathogenic in immuno-compromised patients and may proliferate in the sinonasal cavity [1]. Diseases such as hematological malignancies, aplastic anemia, haemochromatosis, uncontrolled diabetes and AIDS, which cause neutrophilic dysfunction, are among the risk factors [1]. The most common predisposing factor in pediatric patients is hematological malignancies; children with leukemia appear to have higher risk of infection [2]. In immuno-compromised patients, inhaled sporangiospores germinate to form hyphae, could spread to the paranasal sinuses and subsequently to the orbit, meninges, and the brain by direct extension [3].

Mucormycosis is relatively uncommon, with an incidence of 1.7 cases/million, occurring approximately 10- and 50-fold less frequently than invasive aspergillosis and candidiasis. The male to female ratio of affected patients is approximately 2:1, suggesting a male predisposition to this infection [2].

Mucormycosis is emerging as a life-threatening infection associated with severe morbidity and high mortality, caused by the progression of the underlying systemic disease and complications, despite local control of the infection [2]. It may present clinically as rhino-orbital-cerebral mucormycosis (RCM), in a pulmonary, disseminated, gastrointestinal and/or cutaneous form, with different patterns in pediatric and adults. Pediatric cases are 18% of all cases and are characterized histopathologically by the presence of hyphal invasion within the sinus mucosa, submucosa, blood vessels, or bones [4]. Initial symptoms are generally nonspecific and can include: fever, facial pain, rhinorrhea and nasal congestion. The intracranial and orbital involvement could be associated with the onset of ophthalmoplegia, proptosis, orbital cellulitis, vision failures and changes in mental behavior [1].

The standard medical treatment for RCM includes surgical debridement, systemic antifungal treatment mainly with amphotericin B (AmB) and prompt treatment of the underlying systemic disease [2].

Considering that delayed diagnosis, the side effects of AmB treatment and the pres-

## Case Report

ence of underlying systemic disease are factors inducing worse prognosis, it is obvious that early diagnosis and correct management of RCM patients are necessary.

In this paper, we describe the contribution of [ $^{18}\text{F}$ ]2-fluoro-2-deoxy-D-glucose positron emission tomography/ computed tomography ( $^{18}\text{F}$ -FDG PET/CT) in diagnosis and management of an adolescent with invasive RCM.

## Case report

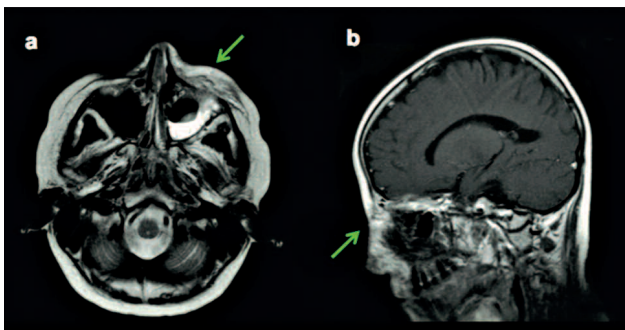
A 13 years old girl was referred to our department after chemotherapy for acute lymphatic leukemia. Chemotherapy was completed three months after a left periorbital swelling associated with facial pain had appeared.

For the suspect of a generalized disease, a MRI scan was performed that showed left orbital soft tissues oedema, signs of left maxillary sinusitis, ethmoiditis and left frontal lobe cerebritis (Figure 1).

Other symptoms were absent and microbiological cultures on nasal, pharyngeal, blood, bladder and rectal swabs were negative. A nasal conchae surgical sweeping revealed fungal hyphae, characteristic of mucormycosis (Figure 2). Meanwhile the patient underwent a CT scan for evaluation of bone involvement, but it didn't show any additional information as compared to MRI.

Two days later she had a  $^{18}\text{F}$ -FDG PET/CT scan (Figure 3) that showed irregular uptake of the radiopharmaceutical in bones and soft tissues from the left frontal and ethmoidal sinuses up to the brain left frontal lobe and also in the maxillary sinus and turbinates up to the back orbital region (SUVmax 7.8), characterized by a central necrotic area. The rest of the whole-body scans was normal.

A systemic AmB treatment started at 1mg/kg/24h and, after 4 weeks, MRI and  $^{18}\text{F}$ -FDG PET/CT were performed again to assess the response to treatment. MRI showed reduction of oedema apparently suggestive of response to treatment, and signs of necrosis in the left emivolto and cerebritis in the left frontal lobe (Figure 4). On the contrary,  $^{18}\text{F}$ -FDG PET/CT showed progression of the disease with more uptake, with increased necrosis and more distorted morphology in the left emivolto lesion (SUVmax 12.4) (Figure 5).

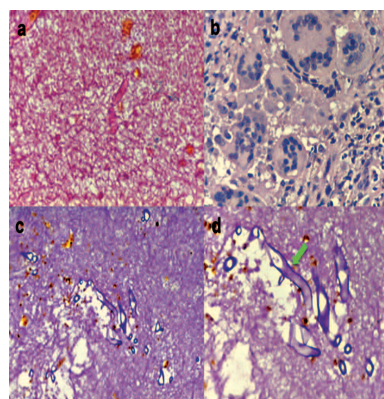


**Figure 1.** Post contrast T1-weighted (MRI) transaxial (a) and sagittal (b) images show left orbital soft tissues oedema (green arrows), signs of left maxillary sinusitis, ethmoiditis and left frontal lobe cerebritis.

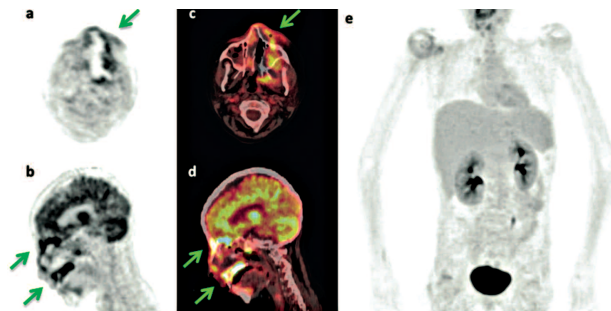
The rest of the whole-body scan showed  $^{18}\text{F}$ -FDG uptake in the skeleton, due to activation of bone marrow as a consequence of AmB nephrotoxicity. Treatment with AmB was then replaced with posaconazole but the patient succumbed three months later.

## Discussion

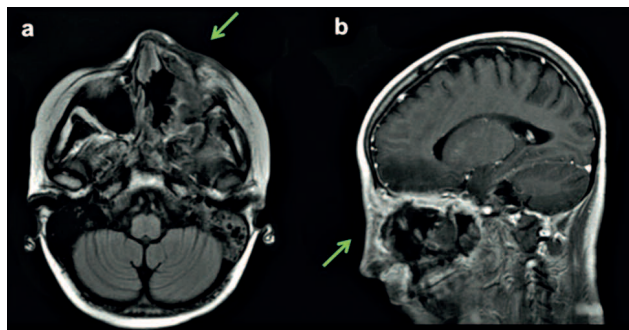
The importance of early diagnosis and therapeutic intervention was recently demonstrated by Chamilos et al (2008), who found that a delay in initiation of AmB treatment in patients who were later found to have RCM was associated



**Figure 2.** Hematoxylin & eosin stain at original magnification 200x (a) and 400x (b) of the nasal conchae surgical sweeping revealed mucorhyphae in necrotic debris and giant cell granulomatous inflammation. PAS stain at original magnification 200x (c) and 400x (d) revealed irregularly and ribbon-like shaped hyphae (green arrow) and spores.

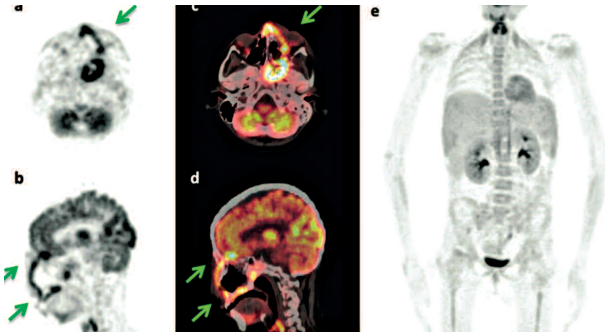


**Figure 3.** Transaxial and sagittal PET and fused images (a, b, c, d) showed bones and soft tissues  $^{18}\text{F}$ -FDG uptake (green arrows) from the left frontal and ethmoidal sinuses up to the brain left frontal lobe, to the maxillary sinus and turbinates, up to the back orbital region (SUVmax 7.8), with a central necrotic area. The whole-body MIP image (e) showed tenuous  $^{18}\text{F}$ -FDG uptake in the right shoulder due to tendinitis.



**Figure 4.** MRI post contrast T1-weighted transaxial (a) and sagittal (b) images showed the reduction of oedema and signs of necrosis in the left emivolto (green arrows) and cerebritis in the left frontal lobe of the brain.

## Case Report



**Figure 5.** Transaxial and sagittal PET and fused images (a, b, c, d) showed progression of the disease; more increased uptake in the left emivolto lesion (SUVmax 12.4) indicating changes in morphology due to the necrosis enlargement (green arrows). The whole-body MIP image (e) showed  $^{18}\text{F}$ -FDG uptake in the skeleton, due to activation of bone marrow as a consequence of AmB nephrotoxicity.

with a significant increase in overall mortality [3].

At present, the imaging diagnosis of RCM relies on investigations such as conventional CT and MRI. These methods may not be sensitive enough for fungal lesions that involve subcutaneous tissues or bones and may show variable imaging patterns [5].

Howells et al (2001), in their review about fulminant invasive fungal rhinosinusitis stated that the initial radiologic diagnostic procedure also in RCM should be MRI because of the low specificity and underestimation of the disease on the CT scan [6]. In our case, MRI and CT were performed only at the initial stage and showed similar information about disease extension.

The known MRI early radiologic findings of RCM are: unilateral mucosal thickening and inflammatory soft tissue lesions in the sinonasal tract [7], as have been described in our patient. As the disease progresses, bone destruction and extra sinonasal extension can be seen by MRI, but only in 20%-50% of RCM cases. Absence of these findings may lead to a delay in diagnosis [7].

The MRI signal intensity of mucormycosis lesions tends to be isointense or hypointense in all sequences. After the administration of gadolinium the lesions had variable enhancement patterns ranging from homogeneous to heterogeneous or non-enhancing at all. Contrast-enhanced T1-weighted images are helpful in delineating the intracranial spread when meningeal enhancement is present as well as in identifying invasion of the cavernous portion of the internal carotid artery, by the disease [5].

Seo et al (2008) confirmed in a study of 23 patients with acute invasive fungal sinusitis (10 of which had RCM) suggested that MRI should be performed as soon as possible and all signs should be recognized [8].

Only MRI was repeated in the following stage as suggested by the literature [5].

The differential diagnosis should consider: other fungi, Graves' disease, carotid cavernous fistula and thrombosis, bacterial cellulites, inflammatory pseudotumor, and paranasal sinus tumor [7].

The  $^{18}\text{F}$ -FDG PET/CT scan is emerging as a useful tool for detecting inflammatory and infectious processes, that could overcome the limits of the imaging modalities mentioned above [9, 10]. The usefulness of  $^{18}\text{F}$ -FDG PET/CT for the diagnosis of RCM is reported in the literature in a limited number of patients [7]. This modality is able to detect active functional/metabolic changes reflecting inflammatory cells activity before the onset of anatomical abnormalities assessed with the conventional radiological modalities and has at least the same sensitivity as these modalities have. In addition,  $^{18}\text{F}$ -FDG PET/CT is able to detect more infectious [11], as in the case we have presented in which  $^{18}\text{F}$ -FDG PET/CT additionally, revealed orbital involvement.

Hot et al (2011) in a study of 30 patients with invasive fungal sinusitis including 2 cases of RCM, reported that, although  $^{18}\text{F}$ -FDG PET/CT showed high sensitivity in RCM, its specificity remained to be determined, especially for discriminating inflammatory granulomatous disease from malignancy [11].

Furthermore,  $^{18}\text{F}$ -FDG PET/CT providing whole body imaging, can give prompt functional information useful for the assessment of the overall therapeutic response [11].

*In conclusion*, our case indicated that  $^{18}\text{F}$ -FDG PET/CT could be considered useful for the diagnosis and response to treatment of RCM.

*The authors declare that they have no conflicts of interest.*

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