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Case Report

Intracranial Leptomeningeal Carcinomatosis: A Diagnostic Study with ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

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Keywords
Leptomeningeal carcinomatosis · ^{18}F-FDG PET · Computed tomography

Abstract
Leptomeningeal carcinomatosis (LC) diagnosis is based on cerebrospinal fluid (CSF) cytological analysis and contrast-enhanced magnetic resonance imaging (MRI); however, low sensitivity was evidenced in some cases delaying prompt and adequate treatments. Brain ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) was also employed in doubtful cases. We retrospectively described 4 suspected LC cases with uncertain or undetectable MRI and initially negative CSF cytology. Whole-body (WB) and brain ^{18}F-FDG PET/computed tomography (CT) were used, the latter showing intracranial tracer uptakes suspected for LC in 3/4 cases. In 2 of these 3 cases, WB scan also evidenced spinal cord lesion and pulmonary tumor, respectively, while both procedures were true negative in the fourth case. CSF cytology became positive after repeated exams in the 3 PET/CT-positive cases. In 1 of these 3 patients, it was also confirmed at MRI, while it stayed negative in the

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remaining PET/CT-negative case with uncertain MRI. ^{18}F-FDG PET/CT could be a useful supportive diagnostic tool in doubtful intracranial and spinal LC.

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Introduction

Leptomeningeal carcinomatosis (LC) is a secondary infiltration by neoplastic cells in the meningeal space. It represents a relatively rare complication that has been observed in 1–5% of patients with solid tumors and in 5–15% of patients with leukemia and lymphomas [1, 2]. Breast and lung carcinomas and melanoma are the most common primary tumors that metastasize in meningeal space, while the most frequent histological type among solid tumors is represented by the adenocarcinoma [2]; in particular, breast tumor is the most common solid tumor to show leptomeningeal metastatic diffusion and it is frequent for most patients to have intraparenchymal brain metastases concurrent with LC and widely disseminated cancer. Generally, LC represents the final phase of metastatic dissemination (>70%), but in 20% of cases it was diagnosed after a period of free diseases or, occasionally (5–10% of cases), it could be the first clinical evidence of tumor presence also without other general symptoms [3–5]. LC is characterized by a poor prognosis, especially if derived from solid tumors, the survival being between 6 and 8 weeks in absence of treatment [6], mainly depending on patient general conditions. However, there are numerous studies that have pointed out that adequate therapeutic approaches, stabilizing neurological symptoms, can improve patient clinical conditions; moreover, the combined use of systemic and local treatments seems to give benefits in terms of survival [7–9], especially in patients with breast cancer with a median survival of 7–12 months [10].

Before any therapy, when LC from a solid tumor is suspected, magnetic resonance imaging (MRI) is necessary for its identification [7], and some studies have reported that cranial and spinal MRI with contrast medium can evidence enhancing lesions in about 70–80% of cases [11, 12].

However, the definitive diagnosis can be achieved only by the cytological analysis of cerebrospinal fluid (CSF), which represents the gold standard [7].

CSF exams are reported positive in approximately 70–90% of LC, even if the diagnosis after the first lumbar puncture is achieved in only 50–60% of cases; thus, further evaluations are often needed to improve the sensitivity (85–90%) of the procedure [13].

Moreover, among the diagnostic imaging procedures, brain ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{11}C-methionine positron emission tomography (PET) and PET/computed tomography (CT) [14, 15], have also been employed in LC diagnosis; however, up to date, only few cases of spinal and intracranial LC have been reported, more frequently derived from breast and lung cancers, all with positive results suspected for LC, and confirmed by repeated CSF cytology exams positive for tumor cells [14, 15]. Furthermore, in some cases reported in different studies with negative CSF for tumor cells, the presence of distant bone metastases at whole-body (WB) CT and ^{18}F-FDG PET, which is known to have remarkably improved the management of cancer patients, was sufficient to clarify leptomeningeal lesion as LC [16, 17]. More recently, a patient with LC has also been described in whom only ^{18}F-FDG PET/MRI was able to achieve the diagnosis, while MRI, CT, and CSF cytology were negative for malignancy [18]; in this case submitted to 2 cycles of intrathecal methotrexate, PET/MRI was also useful to ascertain a reduction of FDG uptake in leptomeningeal lesions after treatment.

In the present study, we retrospectively described 4 consecutive patients who underwent both WB and brain ^{18}F-FDG PET/CT for clinical suspicion of LC as the only metastatic

site from solid carcinomas; MRI was uncertain or not executable for technical reasons, and CSF was initially negative for tumor cells.

Materials and Methods

All patients underwent PET/CT procedures after 370 MBq i.v. injection of ^{18}F-FDG using PET/CT tomography (Discovery 710 GE Medical System); the patients were in a fasting condition for 6 h and with normal blood sugar levels; they remained resting with their eyes closed and with the lights turned off prior to the PET scan. First, brain PET/CT was performed 45 min after injection with acquisition of 15 min and immediately followed by WB scan with acquisition of approximately 20 min. Low amperage for attenuation correction was used for CT data. CT (brain parameters: 3.75-mm slices, 120 kV and 45 mAs; WB scan parameters: 5-mm slices, 120 kV and 60 mAs) was acquired without administration of i.v. contrast agent. After CT, PET was obtained covering the identical transverse field of view. The acquisition time was 2.30 min for table position. PET image data sets were reconstructed iteratively using CT data for attenuation correction, and co-registered images were displayed on a workstation (Advantage GE Medical System) allowing visualization of PET and CT images separately or in fusion mode in the axial, coronal, and sagittal planes. A focal tracer uptake was considered pathological when it was visually noted to be more elevated than background.

The retrospective study was performed in accordance with the regulation of Institutional Review Board and in accordance with the Declaration of Helsinki. Routinely, before PET procedure, written informed consent was given by all patients whose data were treated in accordance with local privacy rules and regulations.

Results

Case 1

A 45-year-old female patient with breast G3 infiltrating ductal carcinoma underwent quadrantectomy and homolateral axillary dissection (pT2pN3aM0) followed by 6 cycles of chemotherapy and local radiotherapy over the chest and adjuvant chemotherapy per os. Bone scintigraphy and WB CT scan performed for staging, were initially negative. After 24 months from the last cycle of therapy, the patient referred hypothymic crisis, headache, nausea, reduction of vision and hearing, mental confusion, and aphasia.

Contrast-enhanced brain MRI and MRI angiography evidenced irregular defects in the superior sagittal sinus with partial thrombosis and a hyperintense area in the left angular gyrus that was initially classified as ischemic lesion. ^{18}F-FDG brain PET/CT was then performed, and it evidenced numerous focal areas of high tracer uptake scattered in different sinuses, such as those sagittal (both superior and lower), rectum and sigmoid, all of these bilaterally, as well as those transverse and sphenoparietal of the left hemisphere of the brain (Fig. 1). These foci were highly suspicious for the presence of LC. In addition, a total body ^{18}F-FDG PET/CT showed a large area of elevated metabolic activity in the medullary channel at the height of the twelfth dorsal vertebra; this area was confirmed as solid expansive lesion on MRI.

Finally, the diagnosis of LC was confirmed by additional CSF cytology after the second lumbar puncture, being the first negative for tumor cells. Cytology evidenced the presence of

lymphocytes and numerous clusters of cells with hyperchromatic nuclei, acanthosis, and eosinophilic cytoplasm; immunohistochemical evaluation revealed positivity for CAM 5.2. The cells were compatible with the clinical suspicion of breast cancer metastases.

Case 2

A 67-year-old female patient, in apparently good health, referred headache, diplopia, dysgeusia, and insomnia, without other clinically general symptoms. An initial brain CT without contrast enhancement to ascertain hemorrhagic or ischemic lesions was negative for pathologic alterations. A WB CT evidenced an area of consolidation in the lower lobe of the left lung, suspected for tumor, although the results of bronchial aspirates were nonspecific. Brain MRI was performed, and it indicated, in flair and T2 acquisitions, some focal areas of altered hyperintense signal of gliotic vascular significance in the white matter of frontal lobes, bilaterally. ^{18}F-FDG brain PET/CT was then performed followed by a WB ^{18}F-FDG PET/CT. The former procedure evidenced numerous foci of intense metabolic activity in parieto-occipital and calcarine sulcus bilaterally that partially involved the longitudinal cerebral fissure (Fig. 2), highly suspicious for LC. Moreover, WB scan evidenced a pulmonary focus of high ^{18}F-FDG uptake (SUV max: 7.14) corresponding to the lesion ascertained at diagnostic CT (the patient was a heavy smoker). However, CSF cytology after the first lumbar puncture was negative. Anyway, neurological symptoms rapidly worsened while high-dose steroids were injected to reduce patient intracranial pressure; thus, the brain MRI was repeated within 2 weeks from the first exams and, at this time, some neoplastic lesions appeared in accordance with PET results. The patient underwent 2 further lumbar punctures and, after the last one, CSF cytology evidenced same pleomorphic elements with hyperchromic nucleus rarely in mitosis or multinucleated. At immunohistochemical evaluation, these elements were positive for cytokeratin CAM 5.2, CK7, and TTF1, but negative for CD56, synaptophysin, and CD45. This cytological aspect can be indicative for adenocarcinoma origin and, in particular, for pulmonary carcinoma due to focal positivity for TTF1. The disease had a dramatic evolution, and the patient died approximately 50 days after the appearance of initial leptomeningeal symptoms. Thus, a definitive histological diagnosis of pulmonary carcinoma, of which LC was apparently the only site of distant metastasis, was not possible.

Case 3

This case was a 70-year-old male patient with costal chondrosarcoma excised at surgery. Thirteen months after treatment, the patient referred frequent hypothymic crisis with sweating and loss of consciousness, memory disorders, mental confusion, and episodes of hypothermia. The patient was hospitalized in the Department of Neurology, where the absence of proprioceptive reflexes in all four limbs was ascertained and, because of a serious hypothymic crisis, was subjected to the insertion of a pacemaker. A dynamic Holter EEG was also performed showing the presence of electroclinic crises with sequences of delta and theta pointed activity and slow activity in PO complexes in the frontotemporal sector of the right cerebral hemisphere, and the patient was treated with antiepileptic drugs.

Contrast-enhanced WB CT was negative for secondary tumor lesions and brain CT excluded densitometric alteration in over- and under-brain encephalic structures; brain MRI could not be performed because of the presence of the pacemaker.

Both WB ^{18}F-FDG PET/CT and brain PET/CT were then performed, the latter evidencing some focal areas of elevated tracer uptake in Brodmann areas 2, 4, and 5 in the superior parietal lobule, in the angular gyrus and the precuneus of both hemispheres as well as in the

left limbic area highly suspicious for LC (Fig. 3). However, the WB ^{18}F-FDG PET/CT was negative for the presence of areas of elevated metabolic activity in other organs or apparatuses of pathological significance.

Finally, the diagnosis of LC was confirmed by repeated CSF cytology evaluations evidencing numerous cells with atypical mitosis suggestive for neoplastic cell dissemination.

Case 4

Case 4 was a 33-year-old female patient with G2 infiltrating ductal breast cancer already surgically treated by quadrantectomy and axillary dissection (pT1pN1M0), followed by 6 cycles of chemotherapy and local radiotherapy over the chest and also treated with adjuvant chemotherapy per os. After 4 years from the last cycle of therapy, the patient referred headache, nausea, and mental confusion. The patient was hospitalized in the Department of Neurology, where bilateral sixth nerve palsy appeared with eye movement disorders, and a diabetes mellitus condition and celiac disease were ascertained. Serological data showed elevated erythrocyte sedimentation rate and leukocytes, normal C-reactive protein, negative C3 and C4 complement tests, positive antinuclear antibodies, and negative anti-neutrophil cytoplasmic antibodies. Contrast-enhanced brain MRI and MRI angiography evidenced a widespread pachy-meningitis and a defect of transverse left venous sinus as venous thrombosis.

The patient was submitted to anticoagulant therapy and was treated with insulin for diabetes mellitus, and a gluten free diet was started. Lumbar puncture with CSF evaluation was performed and rare lymphocytes were evidenced.

Despite anticoagulant therapy, neurological symptoms persisted. Thus, a second brain MRI and MRI angiography were performed after 10 days from the previous exams and the cerebral alteration remained unchanged, thus considered uncertain. High-resolution CT of the chest was negative for pathological lesions.

^{18}F-FDG brain PET/CT excluded the presence of foci with elevated tracer uptake of pathological significance, while WB ^{18}F-FDG PET/CT evidenced a focus of slightly elevated uptake (SUV max 2.13) corresponding to a lymph node in left inguinal region not evidenced in a previous ultrasound exam; the biopsy of the lymph node excluded pathological alterations. Afterwards, repeated CSF cytology evaluations confirmed the presence of lymphocytes and excluded neoplastic cells. Thus, LC was excluded.

Discussion

LC, generally characterized by a poor prognosis, needs an early diagnosis in order to establish the most adequate treatments that, though palliative, could improve the clinical conditions and life expectancy of the affected patients. However, the variability of clinical signs and symptoms makes the diagnosis extremely difficult and, although the detection of neoplastic cells in CSF represents the gold standard, its positivity at the first CSF sampling is low, and often repeated exams are necessary to confirm the diagnosis of LC [19]. Frequently, MRI also with contrast enhancement was performed to ascertain LC and, it has been reported that this procedure can evidence the intracranial meningeal involvement with a sensitivity of 65–70% [20] and a specificity of 77% [21, 22]. However, MRI is often performed when clinical symptoms of metastatic lesions are already present.

Although up until now ^{18}F-FDG PET has been employed in few cases, different authors suggested its use as a supportive technique in intracranial LC diagnosis [23], either using ^{18}F-FDG [14, 16, 17] or ^{11}C-methionine [15] as radiotracers, especially when MRI and CSF

data were initially inconclusive [14, 16, 17]; the evidence of an intense tracer uptake could be highly suspicious for LC, even if not specific, being present also in inflammatory disorders (infectious meningitis, neurosarcoidosis, etc.). Moreover, PET/CT could also be a valid alternative diagnostic tool as imaging procedure when contrast MRI cannot be performed for technical reasons, for instance in a patient with a pacemaker, as reported in the present study, but also in patients in whom the precarious health conditions may prevent lumbar punctures for CSF evaluation.

In the patients described in the present study, a positive ^{18}F-FDG PET/CT has permitted to suspect LC in 3 cases, which was confirmed by the presence of tumor cells after repeated cytological evaluations of CSF. It was also confirmed in 1 of these 3 patients at a repeated MRI, while the latter remained uncertain in another case. However, MRI was not performed in the remaining patient because of the presence of a pacemaker; in contrast, a negative ^{18}F-FDG PET/CT permitted to exclude leptomeningeal metastatic sites in the fourth patient in whom the presence of neoplastic cells in CSF had also been excluded after repeated lumbar punctures, while MRI remained uncertain.

Moreover, the combined use of WB and brain ^{18}F-FDG PET/CT could provide more comprehensive information of the disease than the use of WB PET/CT alone; in our cases, the two procedures were able to ascertain both LC and primary tumor or other metastatic lesions, when CSF cytology was initially inconclusive and MRI uncertain, thus early suggesting a more correct diagnosis. The identification of LC by ^{18}F-FDG PET/CT is even more important when the disorder represents the only metastatic localization, as it has been observed in all cases of the present report.

Furthermore, ^{18}F-FDG seems to be preferred to ^{11}C-methionine even if for the latter the uptake by normal brain parenchyma is lower compared with ^{18}F-FDG, because to use methionine it is absolutely necessary to have a cyclotron in one's own nuclear medicine center, and the half-life of ^{11}C is very short (20 min) unlike that of ^{18}F (110 min), permitting also external supplies of the ^{18}F-FDG.

Finally, a wider use of both WB and brain ^{18}F-FGD PET/CT may be suggested in the diagnosis of LC, in particular when the other diagnostic tools of reference result uncertain or not practicable or initially negative.

Statement of Ethics

The retrospective study was performed in accordance with the regulation of Institutional Review Board and in accordance with Helsinki Doctrine. Routinely, before PET procedure, written informed consent has been obtained by all patients whose data were treated in accordance with local privacy rules and regulations.

Disclosure Statement

Any editorial or financial conflict of interest is excluded.

References

1 Chamberlain MC, Kormanik PR: Carcinomatous meningitis secondary to breast cancer: predictors of response to combined modality therapy. J Neurooncol 1997;35:55–64.

2 Dudani S, Mazzarello S, Hilton J, Hutton B, Vandermeer L, Fernandes R, Ibrahim MFK, Smith S, Majeed H, Al-Baimani K, Caudrelier JM, Shorr R, Clemons M: Optimal management of leptomeningeal carcinomatosis in breast cancer patients – a systematic review. Clin Breast Cancer 2016;16:456–470.

3 Wasserstrom WR, Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer 1982;49:759–772.

4 Grossman SA, Krabak MJ: Leptomeningeal carcinomatosis. Cancer Treat Rev 1999;25:103–119.

5 van Oostenbrugge RJ, Twijnstra A: Presenting features and value of diagnostic procedures in leptomeningeal metastases. Neurology 1999;53:382–385.

6 Herrlinger U, Förschler H, Küker W, Meyermann R, Bamberg M, Dichgans J, Weller M: Leptomeningeal metastasis: survival and prognostic factors in 155 patients. J Neurol Sci 2004;223:167–178.

7 Roth P, Weller M: Management of neoplastic meningitis. Chin Clin Oncol 2015;4:26.

8 Gwak HS, Lee SH, Park WS, Shin SH, Yoo H, Lee SH: Recent advancements of treatment for leptomeningeal carcinomatosis. J Korean Neurosurg Soc 2015;58:1–8.

9 Brower JV, Saha S, Rosenberg SA, Hullett CR, Ian Robins H: Management of leptomeningeal metastases: prognostic factors and associated outcomes. J Clin Neurosci 2016;27:130–137.

10 Chamberlain MC: Neoplastic meningitis. Oncologist 2008;13:967–977.

11 Herrlinger U, Förschler H, Küker W, Meyermann R, Bamberg M, Dichgans J, Weller M: Leptomeningeal metastasis: survival and prognostic factors in 155 patients. J Neurol Sci 2004;223:167–178.

12 Prömmel P, Pilgram-Pastor S, Sitter H, Buhk JH, Strik H: Neoplastic meningitis: how MRI and CSF cytology are influenced by CSF cell count and tumor type. Sci World J 2013;2013:248072.

13 Mack F, Baumert BG, Schäfer N, Hattingen E, Scheffler B, Herrlinger U, Glas M: Therapy of leptomeningeal metastasis in solid tumors. Cancer Treat Rev 2016;43:83–91.

14 Short RG, Bal S, German JP, Poelstra RJ, Kardan A: Potential of F-18 PET/CT in the detection of leptomeningeal metastasis. Neuroradiol J 2014;27:685–689.

15 Padma MV, Jacobs M, Kraus G, Collins M, Dunigan K, Mantil J: 11C-methionine PET imaging of leptomeningeal metastases from primary breast cancer – a case report. J Neurooncol 2001;55:39–44.

16 Carra BJ, Clemenshaw MN: Intracranial leptomeningeal carcinomatosis from breast cancer detected on 18F-FDG PET. J Nucl Med Technol 2015;43:227–228.

17 Ortapamuk H, Demir MK: Intracranial leptomeningeal carcinomatosis in three cases from breast cancer demonstrated on F-18 fluorodeoxyglucose positron emission tomography/computerized tomography. Indian J Nucl Med 2017;32:16–18.

18 Barp A, Cecchin D, Cagnin A: PET/MRI imaging unmasks leptomeningeal carcinomatosis in unexplained diplopia. J Neurooncol 2016;126:205–207.

19 Glantz MJ, Cole BF, Glantz LK, Cobb J, Mills P, Lekos A, Walters BC, Recht LD: Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer 1998;82:733–739.

20 Singh SK, Leeds NE, Ginsberg LE: MR imaging of leptomeningeal metastases: comparison of three sequences. AJNR Am J Neuroradiol 2002;23:817–821.

21 Straathof CS, de Bruin HG, Dippel DW, Vecht CJ: The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. J Neurol 1999;246:810–814.

22 Maroldi R, Ambrosi C, Farina D: Metastatic disease of the brain: extra-axial metastases (skull, dura, leptomeningeal) and tumour spread. Eur Radiol 2005;15:617–626.

23 Komori T, Delbeke D: Leptomeningeal carcinomatosis and intramedullary spinal cord metastases from lung cancer: detection with FDG positron emission tomography. Clin Nucl Med 2001;26:905–907.

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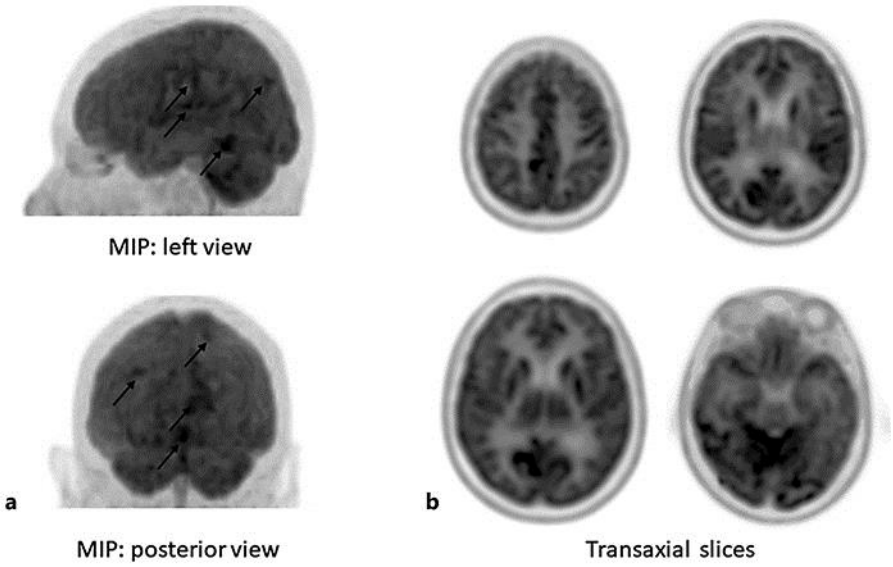

Fig. 1. Maximum intensity projection (MIP) in left and posterior view (**a**) and some representative transaxial slices (**b**) of brain ^{18}F-FDG PET/CT that evidenced numerous focal areas of high tracer uptake (indicated by the arrows in MIP reconstructions) in superior and lower sagittal sinus, rectum and sigmoid sinus, bilaterally, and in transverse and sphenoparietal sinus of the left brain hemisphere.

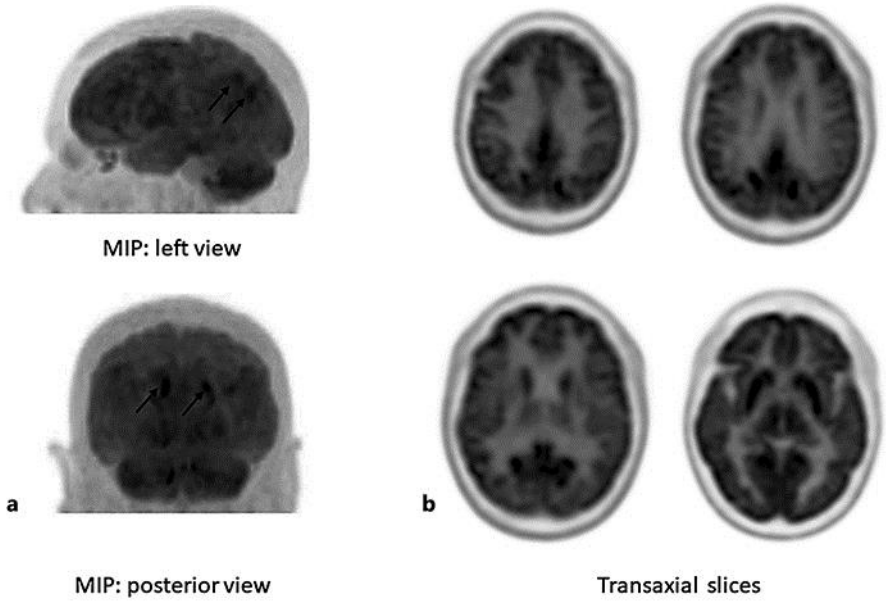

Fig. 2. Maximum intensity projection (MIP) in left and posterior view (**a**) and some representative transaxial slices (**b**) of brain ^{18}F-FDG PET/CT that evidenced numerous foci of intense metabolic activity (indicated by the arrows in MIP reconstructions) in parieto-occipital and calcarine sulcus bilaterally that partially involved the longitudinal cerebral fissure.

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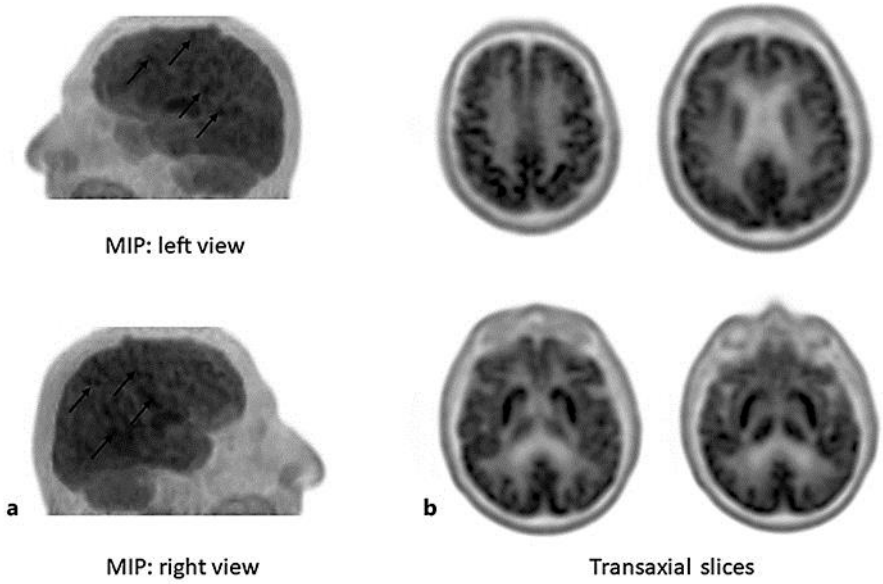

Fig. 3. Maximum intensity projection (MIP) in left and right views (**a**) and some representative transaxial slices (**b**) of brain ^{18}F-FDG PET/CT that evidenced some focal areas of elevated tracer uptake (indicated by the arrows in MIP reconstructions) in Brodmann areas 2, 4, and 5, in the surface of superior parietal lobule, in the angular gyrus, and the precuneus of both hemispheres as well as in the left limbic area.