Fluorine-18-FDG PET/CT in a patient with angiomyolipoma: Response to mammalian target of rapamycin inhibitor therapy

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Abstract
We report on a 27 years old female patient who was referred to our department for whole-body as well as dynamic positron emission tomography/computed tomography (dPET/CT) scan of the upper and middle abdomen with fluorine-18-fluorodeoxy glucose (^{18}F-FDG), for further evaluation of a mass in the left adrenal gland region. Positron emission tomography showed a suspicious, enlarged, hypermetabolic mass with an average standardized uptake value (SUV) of 4.5 and a maximum SUV of 5.9. The patient was referred for biopsy, which revealed an angiomyolipoma, a perivascular epithelioid cell tumor (PEComa) of the adrenal gland. Perivascular epithelioid cell tumors are mesenchymal tumors consisting of blood vessels, smooth muscles and fat cells. The patient received anti-proliferative treatment with Afinitor, a mammalian target of rapamycin (mTOR) inhibitor, and was referred again one month after onset of therapy for early response assessment. The follow-up ^{18}F-FDG PET/CT scan showed a nearly complete resolution of the previously detected adrenal mass, with very low tracer uptake and a decrease in its functional volume. Fluorine-18-FDG PET/CT can be used for treatment response evaluation of angiomyolipoma treated with mTOR-inhibitors.

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Introduction

The differential diagnosis of an adrenal mass includes a variety of benign as well as malignant conditions. Among the benign conditions are pheochromocytomas, adrenal adenomas, adrenal adenomyolipomas, whereas malignant conditions include adrenal carcinomas or metastases from another primary, most commonly the lung [1].

Lesions having a high ^{18}F-FDG uptake in PET/CT are commonly thought to be malignant. In this article we report a case with a malignant-looking intense tracer uptake in the adrenal lesion, which proved to be a benign case of angiomyolipoma. The patient received anti-proliferative therapy with an inhibitor of the mammalian target of rapamycin (mTOR inhibitor; Afinitor). Four weeks after the start of the treatment, ^{18}F-FDG PET/CT was performed for early response assessment and showed a considerable decrease in the tumor activity.

Case Report

A 27 years old, otherwise healthy, female patient presented to the surgical department with the complaint of left-sided flank pain. The pain was not associated with nausea or vomiting. There was no fever. Her feces were regular and normal in color and consistency. Abdominal ultrasound revealed a 9x5cm, well defined, however inhomogeneous mass, lesion in the region of the left adrenal gland. Doppler evaluation of the mass showed high marginal and low internal vascularity. Diagnostic CT showed a well-circumscribed fat-equivalent mass, extending between the left kidney, the spleen, the pancreatic tail and the left colonic flexure. After exclusion of a hormone-producing tumor (pheochromocytoma or adrenal carcinoma) by 24 hours urine and blood tests, sarcoma was considered the most probable diagnosis. The patient was referred to our nuclear medicine department for whole-body dynamic ^{18}F-FDG dPET/CT imaging of the upper

middle abdomen, for further characterization of the mass.

The patient received 226MBq of ^{18}F-FDG as a bolus injection. The PET/CT scanner used (Biograph mCT S128, Siemens Co., Erlangen, Germany) has an axial field of view of 22cm with TruePoint and TrueV, operated in a three-dimensional mode. A low-dose CT (120kV, 30mA) was used for attenuation correction of the PET data and image fusion. One hour after the intravenous tracer injection whole body static scanning was done. All images were iteratively reconstructed with a CT-based attenuation correction software.

Positron emission tomography/CT evaluation was based on qualitative (visual), as well as semi-quantitative assessment (SUV calculation). Visual analysis showed a large, well-circumscribed, hypermetabolic mass in the retroperitoneum, between the left kidney, the left suprarenal and the pancreatic tail. The functional diameter of the lesion was ca. 8x5x9cm. The exact origin of this hypermetabolic mass could not be exactly located. The uptake was intense and homogenous. The average SUV of this mass lesion was 4.5, while the SUVmax was 5.9.

The previously mentioned visual, qualitative and semi-quantitative PET data were suggestive of a highly metabolic tumor, with high clinical suspicion of a retroperitoneal sarcoma. Biopsy, performed for final diagnosis of this mass lesion, revealed a perivascular epitheliod cell tumor of the adrenal glands, most probably angiomyolipoma. In view of the fact that in this patient, the tumor could be surgically removed only by a multivisceral resection procedure (including splenectomy, distal resection of the pancreas combined with colon resection), with the possible risk of the development of an overwhelming post-splenecomy infection (OPSI) syndrome, targeted therapy with the mTOR inhibitor Everolimus (tradename: Afinitor) was started, so that in case of a partial remission, an organ-saving tumor resection could be performed.

The patient received Afinitor (2.5mg/day) for 4 weeks, and PET/CT early response assessment was planned after this time period, so that, in case of response, the therapy would be continued for a total period of 6 months, to further decrease the size of the tumor.

In the follow-up ^{18}F-FDG PET/CT scan, the previously large mass lesion was poorly defined having a decline in its functional volume as well as its metabolic activity. The average SUV had dropped from 4.5 to 2.6, and the maximum SUV from 4.9 to 4.2 (Figure 1).

Discussion

While angiomyolipomas are the most common benign tumors of the kidney, they are extremely rare to be found in the adrenal glands [2] .To our knowledge, only about 10 cases of isolated adrenal angiomyolipomas have been reported so far [3].

Angiomyolipomas are benign tumors consisting of a mixture of blood vessels, bundles of smooth muscles and fat cells. They are considered a subtype of PEComas [4]. Being more common in females, the possibility of a hormonal stimulation of the tumor growth has been suggested [5]. They may present sporadically, as is the case of our patient, or they may be part of tuberous sclerosis complex (TSC). Angiomyolipomas smaller than 4cm are usually asymptomatic and are discovered as an incidental finding during imaging of the abdomen. Larger tumors may present with abdominal pain and carry the risk of severe retroperitoneal hemorrhage and shock. The fat component of the tumor is easily seen on ultrasound. Computed tomography is also very sensitive in differentiating angiomyolipoma from malignant lesions; angiomyolipoma usually demonstrates HU values of less than 20, due to their fat component. However, the fat component of the angiomyolipomas is best demonstrated with fat-suppression techniques on magnetic resonance imaging (MRI).

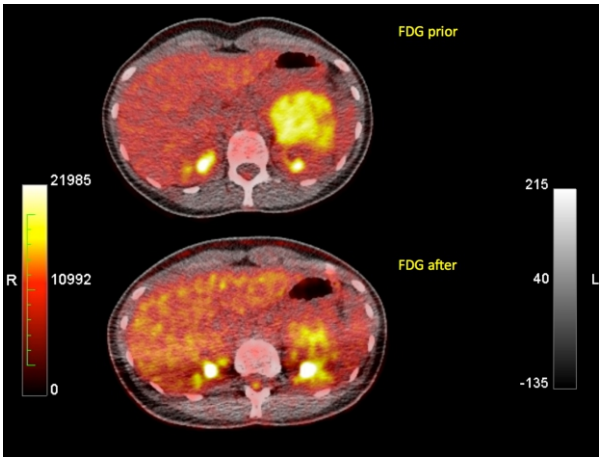

Figure 1. PET-CT transversal images of the upper abdomen prior and after therapy, demonstrating a remarkable decrease in the ^{18}F-FDG uptake at the site of the left adrenal region (site of the suspicious lesion).

While renal angiomyolipomas demonstrate low to very low ^{18}F-FDG uptake on PET/CT scan, which correlates well with their benign nature, many reports have documented intense tracer uptake in angiomyolipomas of the adrenal glands, rendering differential diagnosis from malignant lesions of the adrenals, such as adrenal carcinomas or adrenal metastases, difficult [3]. A possible explanation for the increased ^{18}F-FDG uptake in this benign tumor could be the upregulation of the mTOR pathway, which is involved in several cellular pathways, among which the Glut-1 function [6].

Angiomyolipomas smaller than 4cm usually require no interventions. Larger lesions could be treated by selective embolization or by surgical excision. However, the most novel approach for the treatment of angiomyolipomas, whether sporadic or in association with TSC is the targeted anti-proliferative therapy using mTOR inhibitors. In the body, mTOR is a protein kinase, responsible for the regulation of the abnormal cellular proliferation. In TSC, a mutation in either TSC1 or TSC2 genes results in a decline in the activity of TORC1. This leads to the activation of the mTOR pathway [7]. Consequently, mTOR inhibitors are being studied in the treatment of various conditions, among which are giant cell astrocytomas, angiomyolipomas and pulmonary lesions associated with TSC [8].

Everolimus (Afinitor, Novartis, East Hanover, NJ USA), an mTOR inhibitor, is the most extensively studied drug for the treatment of renal angiomyolipoma. Two randomized controlled trials were conducted, suggesting its efficacy and safety in the control of angiomyolipomas while preserving renal function [9-10]. In the EXIST-2 trial, about 80% of the patients receiving everolimus had a response [10]. Everolimus is now FDA approved for the treatment of angiomyolipomas presenting in the context of TSC. Further clarifications about the optimal duration of anti-proliferative treatment should be studied in order to bring this novel treatment into the clinical setting.

In the here presented case, an adrenal angiomyolipoma patient received a 4 week Afinitor therapy and underwent afterwards a follow-up ^{18}F-FDG PET/CT for treatment response evaluation which demonstrated a remission of the adrenal mass, suggesting that ^{18}F-FDG PET/CT can be helpful in treatment monitoring of angiomyolipomas with mTOR inhibitors.

In conclusion, we present a patient with an adrenal angiomyolipoma, depicted as a highly ^{18}F-FDG avid mass. The patient underwent anti-proliferative treatment with Afinitor, and responded with a considerable drop in the tumor metabolism, within a very short period (4 weeks), as shown in the follow-up PET/CT. Fluorine-18-FDG PET/CT scan can be helpful in treatment response evaluation of angiomyolipomas after mTOR-inhibitor therapy. Further studies to support the role of anti-proliferative treatment in angiomyolipomas should be considered.

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By Prof. Ioannis Tzafetas: Vienna Music Hall was built under the sponsorship of the Greek Nikolaus Dumba and architect the Danish Theophil Hansen. It's Golden Saal has the best worldwide acoustics. The Hall is in Dumbastrasse.