Endokrynologia Polska
DOI: 10.5603/EP.2017.0027
Tom/Volume 68; Numer/Number 3/2017
ISSN 0423–104X

All that glitters on PET is not cancer!

^{18}F-deoxy-glucose avidity versus tumor biology: pituitary incidentaloma in a survivor of two previous unrelated malignancies

Wszystko co świeci w PET nie jest nowotworem złośliwym!
Wychwyt ^{18}F-deoksyglukozy a biologia nowotworu: *incidentaloma* przysadki u chorego, który przebył dwie niezwiązane choroby nowotworowe

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Abstract

Introduction: ^{18}F-deoxy-glucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) is routinely used in the detection of malignant disease based on the property of malignant cells to fuel their growth and replication by increased glucose uptake. Malignant lesions are rare in the sellar region, while pituitary adenomas are the most common pathology. These are benign neoplasms with insidious onset and low proliferation activity, and therefore are only exceptionally detected by ^{18}F-FDG PET/CT. Studies that compare the biology of pituitary adenomas and their radiological properties using PET/CT are still lacking.

Case report: We investigate and discuss tumour biology in light of increased ^{18}F-FDG avidity in a symptom-free, 70-year-old male patient, previously treated for two different malignancies (lung and rectal). Increased tracer accumulation in the sellar region was incidentally detected on a follow-up ^{18}F-FDG PET/CT scan. Additional MRI disclosed pituitary adenoma. Normal hormonal status was found, consistent with the diagnosis of non-functioning pituitary adenoma. Analysis of tumour tissue after pituitary surgery confirmed a silent gonadotroph adenoma with low proliferation index. Low expression of oncogene-induced senescence markers did not support senescence as the explanation for the tumour's low proliferative activity although it was in consonance with the hormonal activity.

Conclusions: Pituitary adenomas can manifest as hypermetabolic foci on ^{18}F-FDG PET/CT imaging with increased tracer uptake even in indolent, clinically silent pituitary adenomas with low mitotic activity. Special attention should be paid to evaluation of ^{18}F-FDG avid pituitary adenomas in patients with multiple malignancies, bearing in mind that avidity does not always mirror its biological behaviour.
(Endokrynol Pol 2017; 68 (3): 352–357)

Key words: *pituitary adenoma; ^{18}F-FDG PET/CT; immunohistochemistry*

Streszczenie

Wstęp: Pozytonowa tomografia emisyjna sprzężona z tomografią komputerową przy użyciu ^{18}F-deoksy-glukozy (^{18}F-FDG PET/CT) to metoda stosowana rutynowo do wykrywania nowotworów złośliwych, opierająca się na właściwościach komórek nowotworowych, których wzrost i replikacja wiąże się ze zwiększeniem wychwytu glukozy. Zmiany złośliwe występują rzadko w okolicy siodła tureckiego, natomiast do najczęstszych patologii należą gruczolaki przysadki. Są to łagodne nowotwory z podstępnym początkiem choroby i małą aktywnością proliferacyjną, dlatego też są wykrywane wyjątkowa rzadko za pomocą badania ^{18}F-FDG PET/CT. Nie przeprowadzono dotychczas badania porównującego cechy biologiczne gruczolaków przysadki i ich właściwości radiologiczne z zastosowaniem techniki PET/CT.

Opis przypadku: Autorzy zbadali i omówili biologię nowotworu w aspekcie zwiększonego wychwytu ^{18}F-FDG u 70-letniego chorego bez objawów, leczonego wcześniej z powodu dwóch różnych nowotworów (płuca i odbytnicy). Zwiększony wychwyt znacznika w okolicy siodła tureckiego wykryto przypadkowo podczas kontrolnego badania ^{18}F-FDG PET/CT. Wykonane dodatkowo badanie MRI ujawniło gruczolaka przysadki. Stężenia hormonów u chorego były w normie, co było zgodne z rozpoznaniem nieczynnego gruczolaka przysadki. Badanie tkanki guza po resekcji chirurgicznej potwierdziło diagnozę niemego klinicznie gruczolaka gonadotropowego o niskim wskaźniku proliferacji. Niska ekspresja markerów starzenia się indukowanego onkogenami nie potwierdziła hipotezy, że starzenie się może tłumaczyć małą aktywność proliferacyjną nowotworu, natomiast była zgodna z aktywnością hormonalną.

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Wnioski: Gruczolaki przysadki mogą być widoczne w badaniu ^{18}F-FDG PET/CT jako ogniska hipermetaboliczne o zwiększonym wychwycie znacznika nawet w przypadku nieczynnych, niemych klinicznie guzów przysadki o małej aktywności mitotycznej. Należy zwrócić szczególną uwagę na ocenę ^{18}F-FDG-awidnych gruczolaków przysadki u chorych z wieloma nowotworami, pamiętając, że intensywność wychwytu znacznika nie zawsze odzwierciedla biologię nowotworu. **(Endokrynol Pol 2017; 68 (3): 352–357)**

Słowa kluczowe: *gruczolak przysadki; ^{18}F-FDG PET/CT; badania immunohistochemiczne*

This work *was supported by the Serbian Ministry of Science (Project number 175033)*

Introduction

Despite the fact that in everyday clinical practice ^{18}F-FDG PET/CT is routinely used for staging of malignant disease, reports on ^{18}F-FDG avid pituitary lesions are exceptionally rare [1–10]. This technique is based on Warburg's phenomenon: malignant cells exhibit increased glucose uptake and break down by mitochondria in order to fuel their growth and replication. The pituitary gland, as highly differentiated endocrine organ, is characterised by low proliferation rate. It does not normally accumulate ^{18}F-FDG and is not visualised on ^{18}F-FDG PET/CT imaging. In differential diagnosis of ^{18}F-FDG avid pituitary lesions, clinical, laboratory, and radiological considerations have to be taken into account. Pituitary adenomas account for more than 90% of all pituitary lesions [11]. Metastases to the sellar region are rare and primary pituitary carcinoma even more so [11–16]. Since ^{18}F-FDG is not a tumour-specific marker its accumulation may also be increased in various inflammatory and granulomatous lesions such as hypophysitis even in patients investigated for malignant disease [17]. Very intense ^{18}F-FDG tracer uptake occurs in the normal cerebral cortex and basal ganglia, since glucose is the predominant substrate for brain metabolism. However, physiological ^{18}F-FDG uptake in the normal pituitary is not a well explored topic. There is no defined consensus for the interpretation of focal ^{18}F-FDG uptake in the pituitary gland [10].

Pituitary incidentalomas, detected on imaging performed for various reasons other than symptoms and signs related to pituitary disease, are a common finding on MRI and CT (4–20% of brain studies) [18] but uncommon on ^{18}F-FDG PET/CT (0.073–0.8%) [9, 10]. Spatial resolution issues on PET/CT may also contribute to reported low incidence because small tumours might be hard to delineate in the background of high tracer activity of the neighbouring brain tissue. Contemporary neuropathology tools can provide new insights into the biology of pituitary adenomas and facilitate clinicopathological correlations important for management and treatment of these patients. In line with this, reports on immunostaining and proliferation markers of ^{18}F-FDG avid pituitary adenomas are lacking.

Here we report, for the first time, discordance between tracer avidity and benign biology and behaviour in a clinically silent ^{18}F-FDG avid pituitary adenoma of gonadotroph origin with low proliferation activity in a patient with two previously diagnosed malignant tumours. In addition, we discuss results of clinical, radiological, hormonal, and pathohistological data of our and fifteen other previously reported patients (three individual case reports and two case series) [1, 3, 6, 9, 10] who underwent pituitary surgery following incidental discovery of ^{18}F-FDG avid pituitary adenomas.

Case report

We report a 70-year-old male patient with previous history of two malignancies and a pituitary incidentaloma detected by ^{18}F-FDG PET/CT. A follow-up ^{18}F-FDG PT/CT was performed after surgery and chemotherapy for adenocarcinoma of the right lung (T2N0M0). Ten years previously this patient underwent surgery followed by chemotherapy for rectal carcinoma (T1N0M0). The last follow-up revealed significantly increased ^{18}F-FDG accumulation in the pituitary gland (Fig. 1). On presentation he was symptom free with no clinical signs of pituitary hormone excess or deficiency, headache, or visual field loss on computerised perimetry. Endocrinological investigation revealed normal hormonal status using commercially available kits (Table I). The patient was free of any signs and symptoms suggestive of metastasis to the sellar region such as polyuria and polydipsia due to insipid diabetes, ophthalmoplegia, visual field loss, headache, or hypopituitarism. Pituitary MRI disclosed homogenous pituitary adenoma measuring 15 × 13 × 10 mm with limited suprasellar extension and no parasellar invasion (Fig. 2). After transsphenoidal pituitary surgery, diagnosis of pituitary adenoma was confirmed. The tumour consisted of monomorphic, epithelial appearing cells with distinct borders in diffuse arrangement, accompanied with occasional perivascular pseudorosettes. Nuclei were uniform, round, with "salt and pepper" chromatin, without conspicuous nucleoli. Mitoses and necroses were not observed. Immunohistochemistry was performed for all anterior pituitary hormones, Ki-67, p53, p16, and p21. Among hormonal markers, positivity was observed only for FSH (Fig. 3A). Proliferative Ki-67 (MIB-1) index was very low (< 0.5%) (Fig. 3B) and tumour cells were p53 negative. The diagnosis of silent gonadotroph

Figure 1. *Frontal* **(A)**, *sagittal* **(B)**, *and coronal* **(C)** *sections on FDG PET/CT scans showing increased accumulation of ^{18}F-FDG tracer in the pituitary gland (SUVmax12.02) compared to adjacent brain tissue structures (SUVmax 8.9)*

Rycina 1. *Obrazy FDG PET/CT w płaszczyźnie czołowej* **(A)**, *strzałkowej* **(B)** *i czołowej* **(C)** *pokazujące zwiększony wychwyt znacznika ^{18}F-FDG w przysadce (SUVmax 12,02) w porównaniu z tkankami sąsiednich struktur anatomicznych mózgu (SUVmax 8,9)*

Table I. ***Hormonal status of our patient***

Tabela I. ***Stan hormonalny chorego***

Hormone	Value	Reference range
Cortisol [nmol/L]	294	113–642
ACTH [ng/L]	14.9	10–90
Prolactin [mIU/L]	318	121–545
FSH [IU/L]	4.2	2.5–15
LH [IU/L]	2.4	2.5–16
Testosterone [nmol/L]	15	8.2–34.8
fT4 [ng/L]	13.6	7–18
TSH [mIU/L]	0.3	0.3–5.5
IGF-I [ng/mL]	202	86–220
GH [mIU/L]	0.33	0–28.5

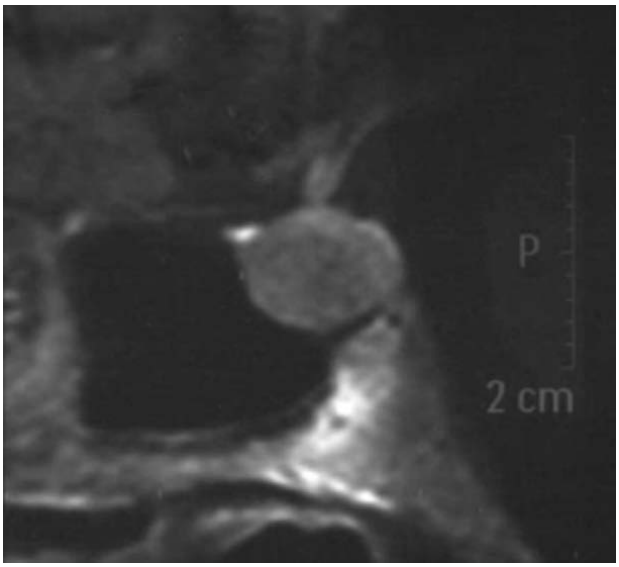

Figure 2. *Sagittal section of sellar region on T1W MRI scan showing isointense pituitary adenoma measuring 15 × 13 × 10 mm*

Rycina 2. *Przekrój okolicy siodła tureckiego w płaszczyźnie strzałkowej na obrazie MRI w sekwencji T1-zależnej z widocznym izointensywnym gruczolakiem przysadki o wymiarach 15 × 13 × 10 mm*

pituitary adenoma was established. Additionally, p16 nuclear positivity was observed in up to 20% of tumour cells, and p21 positivity was present in ≤ 1% of them. Informed consent was approved and signed.

The differential diagnosis of a metastatic sellar lesion, favoured by FDG PET avidity in the context of two

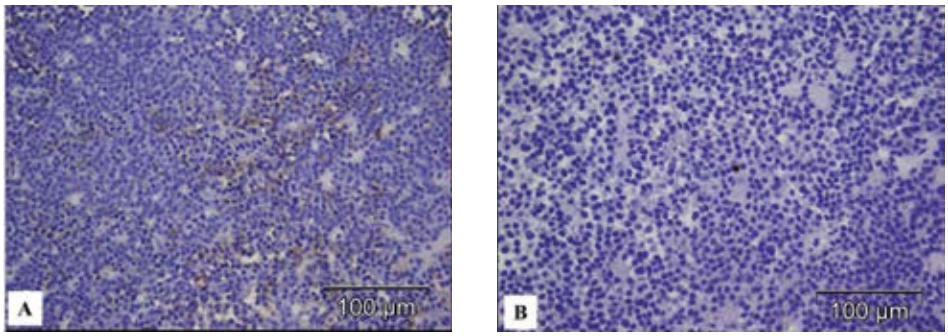

Figure 3A. *Focal moderate FSH immunopositivity. (Magnification × 400).* **B.** *Low proliferative activity is demonstrated by rare, scattered Ki-67 (MIB-1)-positive nuclei. (Magnification × 400)*

Rycina 3A. *Ogniskowa umiarkowanie dodatnia reakcja immunologiczna wobec FSH (powiększenie × 400).* **B.** *Rzadkie, rozproszone jądra z dodatnią ekspresją białka Ki-67 (MIB-1) wskazują na małą aktywność mitotyczną (powiększenie × 400)*

Table II. Characteristics of 18F-FDG avid incidentally discovered pituitary adenomas: clinical, MRI and pathohistology findings (previously published reports and our patient)

Tabela II. Charakterystyka 18F-FDG-awidnych, wykrytych przypadkowo gruczolaków przysadki: parametry kliniczne, wyniki badań MRI i histopatologicznych (publikowane wcześniej dane dotyczące omawianego chorego)

Patient	Age	Sex	Underlying disease	Size on MRI	Symptoms	Hormones	Pathology	[Ref.]
1.	29	M	Thyroid Ca.	Macroadenoma	Headache	↑ GH	GH PA	[9]
2.	55	F	Thyroid Ca.	Macroadenoma	No symptoms	↑ GH	GH PA	[9]
3.	66	M	aortitis	Macroadenoma	Headache	Normal	NFPA	[9]
4.	52	F	MALT lymphoma	Mesoadenoma	Eyelid mass	Normal	NFPA	[1]
5.	50	M	Malignant melanoma	Mesoadenoma	Dizziness	Normal	NFPA	[6]
6.	48	M	Thyroid Ca.	Macroadenoma	No symptoms	Normal	NFPA	[3]
7.	n.r	n.r.	n.r	Macroadenoma	n.r	n.r	PA	[10]
8.	n.r	n.r	n.r	Macroadenoma	n.r	n.r	PA	[10]
9.	n.r	n.r	n.r	Macroadenoma	n.r	n.r	PA	[10]
10.	n.r	n.r	n.r	Macroadenoma	n.r	n.r	PA	[10]
11.	n.r	n.r	n.r	Macroadenoma	n.r	n.r	PA	[10]
12.	n.r	n.r	n.r	Microadenoma	n.r	n.r	PA	[10]
13.	n.r	n.r	n.r	Microadenoma	n.r	n.r	PA	[10]
14.	n.r	n.r	n.r	Microadenoma	n.r	n.r	PA	[10]
15.	n.r	n.r	n.r	Microadenoma	n.r	n.r	PA	[10]
16. (Our patient)	70	M	Lung and Rectal Ca.	Mesoadenoma	No symptoms	Normal	NFPA (FSH+)	

n.r — not reported; GH — growth hormone; NFPA — non-functioning pituitary adenoma; PA — pituitary adenoma; FSH — follicle stimulating hormone; MALT — mucosa associated lymphoid tissue; Ca. — cancer; [Ref.] — reference number; Microadenoma < 1 cm in diameter; Mesoadenoma 1–2 cm in diameter; Macroadenoma > 2 cm in diameter

previous malignancies, was after clinical investigation, MRI imaging and hormonal evaluation made less likely than the working diagnosis of non-functioning pituitary adenoma. The definite diagnosis documented by histopathology and immunohistochemistry was that of a silent gonadotroph pituitary adenoma.

Discussion

The fact that our patient had two independent carcinomas before observed ^{18}F-FDG pituitary avidity, and immunohistochemically verified gonadotroph pituitary adenoma makes our case worth of note.

An increased incidence of pituitary incidentalomas in patients with various malignancies [18, 19] and increased prevalence of malignancy in patients harbouring pituitary adenomas [20] have been reported, suggesting higher pre-test probability for pituitary adenoma than for metastasis in a patient with no pituitary-related symptomatology undergoing whole body ^{18}F-FDG PET/CT for staging of malignant disease.

Recently, two large retrospective studies reported low incidence of incidentally discovered increased ^{18}F-FDG pituitary uptake (0.073% and 0.8%, respectively) [9, 10]. Further analysis of the available data for nineteen out of thirty patients with abnormal pituitary uptakes revealed that an MRI-visible pituitary tumour existed in eleven cases [9]. However, only three of these patients underwent pituitary surgery (two for acromegaly and one for non-functioning pituitary macroadenoma) with the subsequent confirmation of pituitary adenoma pathology (Table II) [9]. In another study twenty-nine clinically significant ^{18}F-FDG avid pituitary lesions were identified (twenty-one pituitary microadenomas, five pituitary macroadenomas, and three metastases to the sellar region from: breast cancer, lung cancer, and non-Hodgkin lymphoma with pituitary involvement) [10]. The diagnosis of pituitary adenoma was confirmed in nine patients with ^{18}F-FDG avid pituitary lesions (five with macro- and four with microadenomas), who underwent transsphenoidal surgery (Table II) [10]. Additionally, three more case reports were published on patients with ^{18}F-FDG avid pituitary adenomas previously treated for malignancy (non-Hodgkin's lymphoma, papillary thyroid carcinoma, and malignant melanoma) in whom non-functioning pituitary adenomas were confirmed after pituitary surgery (Table II) [1, 3, 6]. A recently published study reports on higher sensitivity of ^{11}C-methionine over ^{18}F-FDG for PET/CT in patients with previously diagnosed functioning

pituitary adenomas [21]. This study included 43 patients with functioning pituitary adenomas (15 with Cushing's disease, 16 with acromegaly, and 12 with prolactinomas) most of which were previously operated or treated with gamma-knife, somatostatin analogues (SSA), or dopamine agonists. (DA) [21]. On [18]F-FDG PET/CT, 29 patients of 43 (67%) had positive results with no false positives. [18]F-FDG uptake was positive in 86% of macroadenomas but in only 48% of microadenomas, indicating a considerable prevalence of false negatives. Pre-treatment with DA or SSA was suggested as one of the sources of false negative results. [21]. All patients underwent pituitary surgery, and diagnosis of pituitary adenoma was confirmed by pathology [21]. To the best of our knowledge, none of these published reports and studies included the results of immunostaining for pituitary hormones and proliferation markers.

Contemporary immunohistochemistry is a valuable tool for studying the biology of pituitary adenomas. The low proliferative Ki-67 index in our patient with gonadotroph (FSH+) pituitary adenoma was in sharp contrast to the high [18]F-FDG uptake. These findings suggest that metabolic activity of pituitary adenomas may not necessarily mirror their proliferation activity. In addition, we performed immunohistochemical staining for cell cycle regulators p16 and p21, both being markers of oncogene-induced senescence (OIS). OIS has been proposed as a possible explanation for the prevalently benign behaviour of pituitary adenomas. However, in this patient, a very low prevalence of p16 and p21 positive nuclei, did not support senescence as the explanation for tumour's low proliferative activity, although it was in consonance with the hormonal activity [22, 23]. Importantly, studies that compare the biology of pituitary adenomas and their radiological properties using magnetic resonance and PET/CT are still lacking.

During the two-year follow-up of our patient, his pituitary function remained normal with no residual tumour on MRI in keeping with benign biological properties of his pituitary adenoma. However, further regular MRI follow-up is still indicated, since clinical behaviour is unpredictable. Despite low Ki-67 (< 3%), recurrences can occur after complete resection in 19% of patients operated for non-functioning pituitary adenomas after four years of follow-up [24].

Further advances in the metabolic imaging and receptor status of pituitary neoplasms with specific tracers may be aimed at targeting specific molecular defects responsible for growth, secretory activity, and distinct biological features in different tumour types. This may also have implications for more detailed metabolic and biological profiling of pituitary neoplasms, their treatment and follow-up.

Conclusions

Pituitary adenomas can manifest as hypermetabolic foci on [18]F-FDG PET/CT imaging with increased tracer uptake, in spite of their low mitotic activity. Special attention should be paid to evaluation of [18]F-FDG avid pituitary adenomas in patients with multiple malignancies, bearing in mind that avidity does not always mirror its biological behaviour.

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