The Role of 18F-FDG PET/CT and Single Isotope 99mTc-Tetrofosmin Scintigraphy Combined with SPECT in Diagnosis of Multiple Endocrine Neoplasia Type 1 Syndrome

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Abstract
We present a case of a 47-year-old woman with type 1 multiple endocrine neoplasia, primary hyperparathyroidism, insulinoma, and nonfunctioning pituitary adenoma. In July 2017, the patient was referred to the Department of Nuclear Medicine of St George University Hospital in Plovdiv for a PET/CT scan because of persistent hypoglycemic episodes and high serum insulin levels. A whole-body PET/CT examination was performed 65 min after intravenous application of 188 MBq 18F-FDG on a hybrid PET/CT scanner (Biograph mCT 64, Siemens). We detected a low metabolically active lesion 10 mm in diameter (SUVmax - 2.00), located below the left thyroid lobe suspicious for parathyroid adenoma. In the remaining scanned areas there were no PET/CT data for other areas with increased glucose metabolism with malignant characteristics that could be associated with the underlying disease.

For further characterisation of the lesion, two months later we performed a single-isotope dual-phase 99mTc-tetrofosmin scintigraphy combined with an early SPECT technique on a SPECT gamma camera (SYMBIA E DUAL). The examination visualized a zone of hyperfixation located dorsally to the caudal portion of the left thyroid lobe associated with a hyperfunctioning parathyroid adenoma.

This case allowed us to compare two nuclear medicine modalities with different equipment and radiopharmaceuticals – PET/CT with 18F-FDG and single-isotope dual-phase 99mTc-tetrofosmin scintigraphy combined with an early SPECT in one and the same patient. Different factors can explain the acquired different diagnostic information.

Keywords
99mTc-tetrofosmin scintigraphy, PET/CT 18F-FDG, primary hyperparathyroidism, SPECT

INTRODUCTION

Multiple endocrine neoplasia (MEN) is characterized by the presence of benign or malignant tumours involving two or more endocrine glands. The clinical picture depends on the type of the affected endocrine glands. Each of the syndromes has autosomal dominant pattern of inheritance with high penetrance and variable expression. The most common tumours seen in MEN 1 involve the parathyroid glands, islet cells of the pancreas and the pitu-
Primary hyperparathyroidism (PHPT), which is due to autonomic overproduction of parathyroid hormone (PTH) by one or more abnormal parathyroid glands, is the most common manifestation of MEN 1. In the majority of cases it is asymptomatic. Most of the patients with PHPT have no clinical symptoms and the disease is diagnosed by detected changes in serum calcium, phosphate, and PTH levels. In 85%–90% of patients, the cause for PHPT is a solitary parathyroid adenoma and in the remaining 10%–15% it is due to primary hyperplasia of more than one parathyroid gland. In the past, the standard surgical approach to PHPT was usually bilateral cervical exploration. In recent years, the unilateral cervical exploration with removal of pre-established and topically localized abnormal parathyroid gland has become widespread in clinical practice. Parathyroid scintigraphy with 99mTc-tetrofosmin in combination with ultrasound examination has a well-established role in the preoperative examination protocols in patients with PHPT, especially in cases with abnormal localization of the hyperfunctioning parathyroid adenomas and in cases of recurrence of the disease.

We present a case of a female patient with multiple endocrine neoplasia (MEN) – type 1 in whom whole body PET/CT examination with 18F-FDG showed a lesion with low metabolic activity, suspicious for parathyroid adenoma, behind the left thyroid lobe, which was lately confirmed with single-isotope dual-phase 99mTc-tetrofosmin scintigraphy in combination with an early SPECT technique.

CASE REPORT

The patient was a 47-year-old woman diagnosed over the years with MEN 1 - hormonally inactive pituitary microadenoma, hyperparathyroidism and recurrent hypoglycemic episodes accompanied with high serum insulin levels. The patient has been diagnosed, treated, and followed-up for many years in the Clinic of Endocrinology and Metabolic Diseases at St George University Hospital from where she was referred to the Department of Nuclear Medicine for topical diagnosis. The initial manifestation of the disease dates back to 1999 and was associated with frequent episodes of hypoglycemia with frequent hypoglycemic comas. Due to the lack of any detectable local changes in the pancreas from the performed imaging studies and the presumed presence of beta-cell hyperplasia, a therapeutic resection of the tail and part of the body of the pancreas was performed. Postoperatively, a reduction of the hypoglycemic episodes was reported. Later on, primary hyperparathyroidism was diagnosed due to aggravating bone pain, bilateral nephrolithiasis, and changes in the calcium-phosphate metabolism. In 2000, a surgical removal of an adenoma of the right lower parathyroid gland was performed simultaneously with right lobectomy of the thyroid gland due to benign nodular transformation. The MRI examination of the hypothalamic-pituitary area, performed in 2006, revealed a 4-mm microadenoma of the pituitary gland, functionally assessed as hormonally inactive. The patient’s case was originally presented from an endocrinological point of view at the XI National Congress of Endocrinology.

Due to persistence of clinical and paraclinical data for hyperparathyroidism in 2007, a MRI revealed a formation located in the upper anterior mediatinum. On July 4, 2007, the patient underwent a new operation with extirpation of a parathyroid adenoma 15×10 mm in size. The histological examination showed parathyroid adenoma composed of chief cells and oxyphil cells.

In July 2017, elevated values of total calcium of 2.59 mmol/l (2.2–2.6) and PTH 184 pg/ml (11–67) with a low level of serum phosphate 0.75 mmol/l (0.77–1.45) were registered again. Ultrasound of the cervical region did not reveal any lesions suspicious for parathyroid adenoma, and the patient was left untreated. Because of the appearance again of clinically presented hypoglycemic episodes, with increasing intensity and frequency, accompanied by high levels of serum insulin, despite the previously performed resection of the tail and part of the body of the pancreas, the patient was referred to the Department of Nuclear Medicine at St George University Hospital, Plovdiv for a PET/CT scan. The examination was performed following a strict protocol for preparation of the patient: a fasting period of at least 6 hours, no intake of alkaloid beverages, sweet liquids, without tobacco smoking and strenuous physical activity one day before and on the day of the study. Blood glucose was measured and intravenous catheter was placed. The radiopharmaceutical 18F-fluorodeoxyglucose (FDG) was used for the examination. The patient underwent PET/CT whole-body scan on a hybrid apparatus PET/CT (Biograph mCT64, Siemens.), 65 minutes after intravenous administration of 188 MBq 18F-FDG. A lesion located dorsally of the left thyroid lobe was detected with dimensions of 10 mm and low metabolic activity, SUVmax - 2.00, suspicious for a parathyroid adenoma. (Fig. 1 and Fig. 2) In the remaining scanned areas, including the pancreas, there were no PET/CT data for other areas with increased glucose metabolism that could be associated with the underlying disease.

Because the patient had already undergone two surgical
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removals of parathyroid adenomas in the past and the inconclusive results received by the ultrasound examination of the neck, to elucidate the nature of the discovered lesion behind the left lobe of the thyroid gland, two months later we performed a single-isotope dual-phase 99mTc-tetrofosmin scintigraphy, combined with an early SPECT technique on a SPECT gamma camera “SYMBIA E DUAL”. After administration of 740 MBq 99mTc-tetrofosmin strictly intravenously to the patient, early (20 min) and late (120 min) planar images of the neck and upper mediastinum were obtained. In addition to this procedure, immediately after the early planar images, without changing the position of the patient, we performed SPECT technique. The examination was performed in a tomographic mode with a low-energy collimator in a circular orbit of 360 degrees, “Step and shot” registration, matrix 128×128, 60 projections for 32 seconds at an interval of 30 degrees, for a total of 30 minutes.

We processed the results both from the early phase (20 min) and the late phase (120 min) images together with the images obtained from early SPECT (20 min).

In the early phase (20 min) images, an intensive accumulation of the radiopharmaceutical was registered in the thyroid gland with relatively higher uptake in the caudal part of the left thyroid lobe. (Fig. 3) Early SPECT images showed an area with increased accumulation located dorsally of the caudal part of the left thyroid lobe. The late phase (120 min) images revealed a delayed washout of the radiopharmaceutical, while showing at the same time a focus of a residual activity in the caudal part of the left thyroid lobe. The performed single-isotope dual-phase 99mTc-tetrofosmin scintigraphy

Figure 1. PET/CT with 18F-FDG - axial CT, PET and hybrid images.

Figure 2. Hybrid axial PET/CT image - a lesion located dorsally of the left thyroid lobe is visualized with low metabolic activity, SUVmax - 2.00 which is suspected for a parathyroid adenoma.
combined with early SPECT technique visualized an area of increased accumulation located dorsally from the caudal portion of the left thyroid lobe, which was associated with a hyperfunctioning parathyroid adenoma. (Fig. 4)

DISCUSSION

This case allowed us to compare the results of two nuclear medicine modalities using different equipment and radiopharmaceuticals – PET/CT with 18F-FDG and single-isotope dual-phase scintigraphy with 99mTc-tetrofosmin combined with an early SPECT technique in one and the same patient. Several factors can explain the difference in the obtained diagnostic information.

In the last few years, reports of the use of PET/CT in the detection of parathyroid adenomas have become more frequent. PET with 18F-fluorodeoxyglucose (18F-FDG) was used to detect increased metabolic activity of adenomas with variable success. Some data show that 18F-FDG PET is more sensitive, but less specific than scintigraphy with 99mTc-sestamibi combined with SPECT. Other authors report very low sensitivity of 18F-FDG PET in detecting parathyroid adenoma. The use of PET with 11C-methionine has been studied in some parathyroid adenomas. Sundin et al., using semiquantitative standard values of accumulation (SUV) in 34 patients with primary or recurrent parathyroid adenomas achieved showed positive results up to 85% in PET/CT compared with 59% in CT alone and 57% in ultrasound.

Beggs and Hain used 11C-methionine to examine 51 patients with suspected parathyroid adenomas in whom other imaging methods gave negative or questionable results. Results showed sensitivity of 83% and specificity of 100% with an accuracy of 88%. A major problem with 11C-methionine is its short half-life of 20 minutes, which limits its use only in centres adjacent to a cyclotron.

99mTc-tetrofosmin has some similar properties to 99mTc-sestamibi, although the mechanism of accumulation is different. Its retention occurs mainly in the cytosol rather than in the mitochondria. When used for parathyroid scintigraphy, 99mTc-tetrofosmin shows slower washout from the thyroid gland which makes it unsuitable for single-isotope dual-phase scintigraphy. However, the sensitivity is significantly improved when used in a subtraction protocol and in combination with SPECT technique.
Hiromatsu et al.\textsuperscript{17} aimed to confirm the clinical significance of 99mTc-tetrofosmin scintigraphy for localizing a hyperfunctioning parathyroid gland in patients with primary hyperparathyroidism. All patients were examined 10 minutes and 2 hours after injection of 99mTc-tetrofosmin, with additionally performed ultrasound, CT and MRI. The ratio of accumulation of tetrofosmin in the thyroid and the parathyroid glands was calculated. In conclusion, the authors found that scintigraphy with 99mTc-tetrofosmin is useful for the localization of parathyroid adenomas. The accumulation of the 99mTc-tetrofosmin depends on the weight of the tumour and the serum level of the parathyroid hormone.

The diagnostic value of 99mTc-tetrofosmin for localization of abnormal parathyroid glands in patients with hyperparathyroidism has been studied by Vallejos et al.\textsuperscript{18} They found that 99mTc-tetrofosmin was suitable for pre-operative detection of abnormal parathyroid glands. The early images at 15 minutes were better than those at 120 minutes. 99mTc-tetrofosmin washes out slower from the normal thyroid tissue than 99mTc-sestamibi and both radiopharmaceuticals show better results in comparison with pertechnetate TI-201 subtraction technique.

In their study, Gallowitsch et al.\textsuperscript{19} noted that 99mTc-tetrofosmin appears to be a promising alternative marker with similar abilities to 99mTc-sestamibi in the localization of parathyroid adenomas. SPECT images show clear advantages in terms of sensitivity over planar scintigraphy. This technique should be used in cases with poor or absent accumulation in single-isotope dual-phase method. In areas with endemic goiter, an ultrasound should also be performed to avoid misinterpretation of the results due to prolonged retention of the radiopharmaceutical in existing thyroid adenomas.

Dual-isotope subtraction scintigraphy with 99mTc-tetrofosmin/99mTc-pertechnetate and SPECT are highly sensitive methods for localization of parathyroid adenomas and their combination can further improve diagnostic accuracy.\textsuperscript{20}

99mTc-tetrofosmin, like 99mTc-Sestamibi, is not ideal for localization of hyperplastic glands in secondary hyperparathyroidism because of its low sensitivity.

**CONCLUSIONS**

The various devices (SPECT gamma camera and PET/CT), radiopharmaceuticals - 18F-FDG and 99mTc-tetrofosmin and hybrid methods for examination used in the nuclear medicine have their advantages and disadvantages. In our patient, the use of the single-isotope dual-phase 99mTc-tetrofosmin scintigraphy combined with SPECT technique proved to have higher sensitivity and specificity compared to PET/CT with 18F-FDG. In the cases with clinical and laboratory data for PHPT where there is no possibility for accurate localization of the pathologically changed parathyroid glands by the other diagnostic modalities, 99mTc-tetrofosmin scintigraphy is the method of choice, especially in cases of atypical localization of hyperfunctioning parathyroid adenomas or in cases with a recurrent disease.

**REFERENCES**

Роль ПЭТ/КТ с 18F-FET и сцинтиграфии с моноизотопом 99mTc-tetrofosmin в сочетании с SPECT в диагностике синдрома множественной эндокринной неоплазии 1 типа

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Резюме
Мы представляем случай 47-летней женщины с множественной эндокринной неоплазией 1 типа, первичным гиперпаратиреозом, инсулиномой и дисфункциональной аденомой гипофиза. В июле 2017 года пациент был направлен в отделение ядерной медицины Университетской больницы «Св. Георги» для ПЭТ/КТ-сканера из-за стойких гипогликемических приступов и высокого уровня инсулина в сыворотке. ПЭТ/КТ-обследование всего тела выполняли через 65 минут после внутривенного введения 188 MBq 18F-FET на гибридный ПЭТ/КТ-сканер (Biograph mCT 64, Siemens). Выявлено низкометаболически активное образование диаметром 10 мм (SUVmax - 2,00), расположенное ниже левой доли щитовидной железы с подозрением на аденому надщитовидной железы. В остальных сканируемых областях отсутствовали данные ПЭТ/КТ для других областей с повышенным метаболизмом глюкозы со злокачественными новообразованиями, которые могли бы быть связаны с основным заболеванием.

Чтобы дополнительно охарактеризовать поражение, два месяца спустя мы выполнили одноизотопный двухфазный метод с 99mTc-tetrofosmin в сочетании с ранней методикой SPECT гамма-камеры SPECT «SYMBIA E DUAL». При обследовании визуализировалась зона гиперфиксации, расположенная дорсально в каудальной части левой доли щитовидной железы, связанная с гиперфункционирующей аденомой паращитовидной железы.

Этот случай позволил нам сравнить два ядерных медицинских метода с разными приборами и радиофармпрепаратами – ПЭТ/КТ с одноизотопным 18F-FET двухфазным методом 99mTc-tetrofosmin в сочетании с ранней методикой SPECT гамма-камеры у одного и того же пациента. Различные факторы могут объяснить разницу в диагностической информации.

Ключевые слова
99mTc-Tetrofosmin сцинтиграфия, ПЭТ/КТ с 18F-FET, первичный гиперпаратиреоз, SPECT