Multiple endocrine neoplasia type 2A syndrome (MEN2A) and usefulness of 68Ga-DOTATATE PET/CT in this syndrome.

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Multiple endocrine neoplasia type 2A syndrome (MEN2A) and usefulness of 68Ga-DOTATATE PET/CT in this syndrome.

AIM: *The aim of this study was to evaluate a new imaging method 68Ga-DOTATATE PET/CT as an alternative method to diagnose evidence of neuroendocrine tumors or their metastasis (if any) in patient with MEN 2A.*
METHODS: *Three patients(2F, 1M; age 28,46 and 50 years) with MEN 2A syndrome who underwent 68Ga-DOTATATE PET/CT scan were prospectively evaluated. PET/CT images were analyzed with measurement of maximum standardized uptake value (SUVmax).*
RESULTS: *All patients had adrenal masses with increased uptake of 68Ga-DOTATATE (first case adrenal mass SUVmax: 9,1, second case adrenal mass SUVmax: 32,4(right), 30,3(left) and third case SUVmax:12,4). All of the patients had medullary thyroid carcinoma with increased uptake of 68Ga-DOTATATE (first case SUVmax: 3,3 second case SUVmax:7,7 and third case SUVmax: left thyroid nodule: 19,4, right thyroid nodule: 21,2). Third case has a parathyroid adenoma with SUVmax: 2,8.*
CONCLUSIONS: *New imaging method 68Ga-DOTATATE PET/CT may be an alternative method to diagnose MEN 2A patients. 68Ga-DOTATATE PET/CT can give a great opportunity to detecting the multiple neoplasia like MEN 2A with only one session.*

KEY WORDS: MEN 2A syndrome, 68Ga-DOTATATE PET/CT, Neuroendocrine tumors

Introduction

Classical MEN 2A syndrome(MEN 2A) is characterized by medullary thyroid cancer (MTC), pheochromocytoma, and primary parathyroid hyperplasia. Patients with MEN 2A (and their affected family members) also require screening for MEN 2A associated tumors. In all patients diagnosed with MEN 2A; measurement of plasma fractionated metanephrines and calcitonin (as the initial screening for pheochromocytoma and medullary thyroid cancer) and serum calcium (to rule out hyperparathyroidism requiring concomitant surgical intervention) are required for diagnosis. Patients diagnosed with MEN 2A based upon the classical clinical features and family history evaluation should include RET mutation analysis in order to identify the specific RET mutation to facilitate family screening [1-,4]. Affected family members also require screening for MEN 2A associated tumors [5,6].

The diagnosis of MEN 2A requires imaging results besides biochemical testing [7].

Novel nuclear medicine modalities, including FDG positron emission tomography (PET) and 68Ga DOTATATE PET/CT have been added to the conventional techniques of 123I-metaiodobenzylguanindine (MIBG) scintigraphy, computed tomography and magnetic resonance imaging [8].

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The aim of this study was to evaluate a new imaging method 68Ga-DOTATATE PET/CT as an alternative method to diagnose evidence of neuroendocrine tumors or their metastasis (if any) in patient with MEN 2A.

Methods

Study Design

From January 2017 to August 2018 were prospectively planned use on 68Ga-DOTATATE PET/CT to diagnose MEN 2A.

patient selection

All enrolled patients have given informed consent and the study has been approved by the ethics committee of Dicle University. MEN 2A patients were included in the study. Those who were not diagnosed with MEN 2A were excluded from the study.

Dotatate

68Ga-DOTATATE labelling according to protocol as described in the literature was performed [9]. Whole body images were acquired on a PET/CT scanner (Siemens Biograph 6, Siemens Medical Systems, CTI, Knoxville, TN, USA) 45 to 60 minutes after intravenous injection of (2.7-4.5 mCi) 68Ga-DOTATATE administration. Low dose, contrast CT scan (Biograph 6: 50 mA, 110 kVp) was performed for attenuation correction and anatomical localization. PET scan was acquired in 3D mode from base of skull to mid-thigh. An iodine based oral contrast agent was administered to all patients. CT acquisition was performed on a spiral CT scanner, with a slice thickness of 5 mm and a pitch of 1. After CT scan, 3D-PET images were acquired for 4 min per bed (totally 6–8 beds) in the same position. CT-based attenuation correction of the emission images was used. PET images were reconstructed by the iterative method using ordered-subset expectation maximization (OSEM; two iterations and eight subsets). After completion of the PET acquisition, the reconstructed attenuation-corrected PET images, CT images, and fused images of PET and CT images were reviewed.

Imaging Evaluation

The images were evaluated visually by experienced nuclear medicine physician. Areas of abnormally increased tracer uptake were documented. For semiquantitative analysis of activity, a regions of interest (ROIs) analysis was performed for the lesions on PET images and sizes were calculated for the lesions on CT images.

Results and Patient population

Case 1

A 46-year-old women with a history of diabetes and hypertension for three years. She was treated with insulin and metformin for the treatment of diabetes but received no medication for hypertension. The ultrasound of abdomen showed an adrenal mass on the left side. The patient had been complaining of headaches, perspiration and palpitation. The RET proto-oncogene of the patient was positive. The patient's blood pressure was 160/100 mmHg and pulse rate was 98 per/minute. The complete blood count (CBC), sedimentation, kidney and liver function of the patient were normal. The calcitonin level 1181pg/ml (normal range: 0-11.5) was increased. The patient's PTH level was normal. Twenty four hours urine metanephrine levels was 21767 µg/24 hour (normal range: 52-341µg/24 hour) normetanefrin was 3369 µg/24 hours (normal range: 88-444µg/24), and vanil mandelic acid (VMA) was 65 mg/24hours (normal range: 1.8-6.7mg/24hours). Fine needle aspiration biopsy was performed and thyroid ultrasonography showed hypoechoic solid nodule of 18x10mm in size and containing coarse calcification. Computed tomography scan of the abdomen shows left sided heterogeneous adrenal solid mass of a size 52x60x54mm. The 68Ga-DOTATATE PET/CT imaging showed a left adrenal mass with a high SUVmax (9,1) and there were also increased SUVmax (3,3) at the left lobe of the thyroid. No metastases were found at 68Ga-DOTATATE PET/CT (Figs. 1 A, B)

Case 2

A 50-year-old male patient (the brother of first case) was screened for MEN. Twenty for hour urine metanephrine was 3762 µg/24hour (normal range: 52-341 µg/24hour) and normetanephrine was 1745 µg/24hour (normal range: 88-444µg/24). Bilateral nodular lesions were observed on adrenal imaging. The patient was given preoperative alpha blocker and serum physiological support and was prepared for operation. Thyroid ultrasonography revealed multinodular goiter. The largest nodule was on the left side and hypoechoic. Serum calcitonin level was found to be high 327 pg/ml (normal range: 0-11.5pg/ml). The 68Ga-DOTATATE PET/CT imaging showed bilateral adrenal masses with a high SUVmax (left adrenal SUVmax: 32,4, right adrenal SUVmax 30,3) and there were also increased SUVmax (7.7) at the left lobe of the thyroid (Figs. 2 A, B, C).

The patient underwent bilateral surrenalectomy without any problems. Bilateral adrenal gland pathology was consistent with pheochromocytoma. Chromogranin, synaptophysin, S100 was positively detected.

After surrenalectomy, total thyroidectomy and central lymphatic dissection were performed. Pathology report

was reported as medullary thyroid carcinoma. Immunohistochemical examination of thyroid ectomy material revealed CEA, chromogranin, synaptophysin calcitonin and amyloid positive.

Case 3

A 28-year-old women had right adrenal mass with a diameter of 28x22mm. She had also bilateral thyroid nodules. Twenty for hour urine metanephrine was 3126 µg/24hour (normal range 52-341µg/24hour) and normetanephrine was 1033 µg/24hour (normal range 88-444µg/24hour). Plasma calcium levels was 110.5 pg/ml and parathyroid hormone levels was 167pg/ml.
The 68Ga-DOTATATE PET/CT imaging showed right adrenal mass with a high SUVmax (SUVmax 12,4) and there were also increased SUVmax at the right and left lobe of the thyroid (left thyroid nodule SUVmax: 19,4, right thyroid nodule SUVmax 21,2) (Figs. 3 A, B). There was also a nodular lesion at the inferior of the left thyroid with a diameter of 10 mm. This lesion resembled parathyroid adenoma with a slightly elevated DOTATATE uptake (SUVmax 2.8)
The patient underwent surrenalectomy without any problems. Postoperatively detected urinary catecholamines levels decreased but they were still higher than the normal range. Twenty for hour urine metanephrine was 876 µg/24hour (normal range: 52-341µg/24hour) and normetanephrine was 630 µg/24 hours (normal range: 88-444µg/24). Adrenal gland pathology was consistent with pheochromocytoma.
After surrenalectomy, total thyroidectomy, parathyroidectomy and central lymphatic dissection were performed. Pathology report was reported as medullary thyroid carcinoma, parathyroid adenoma and reactive cen-

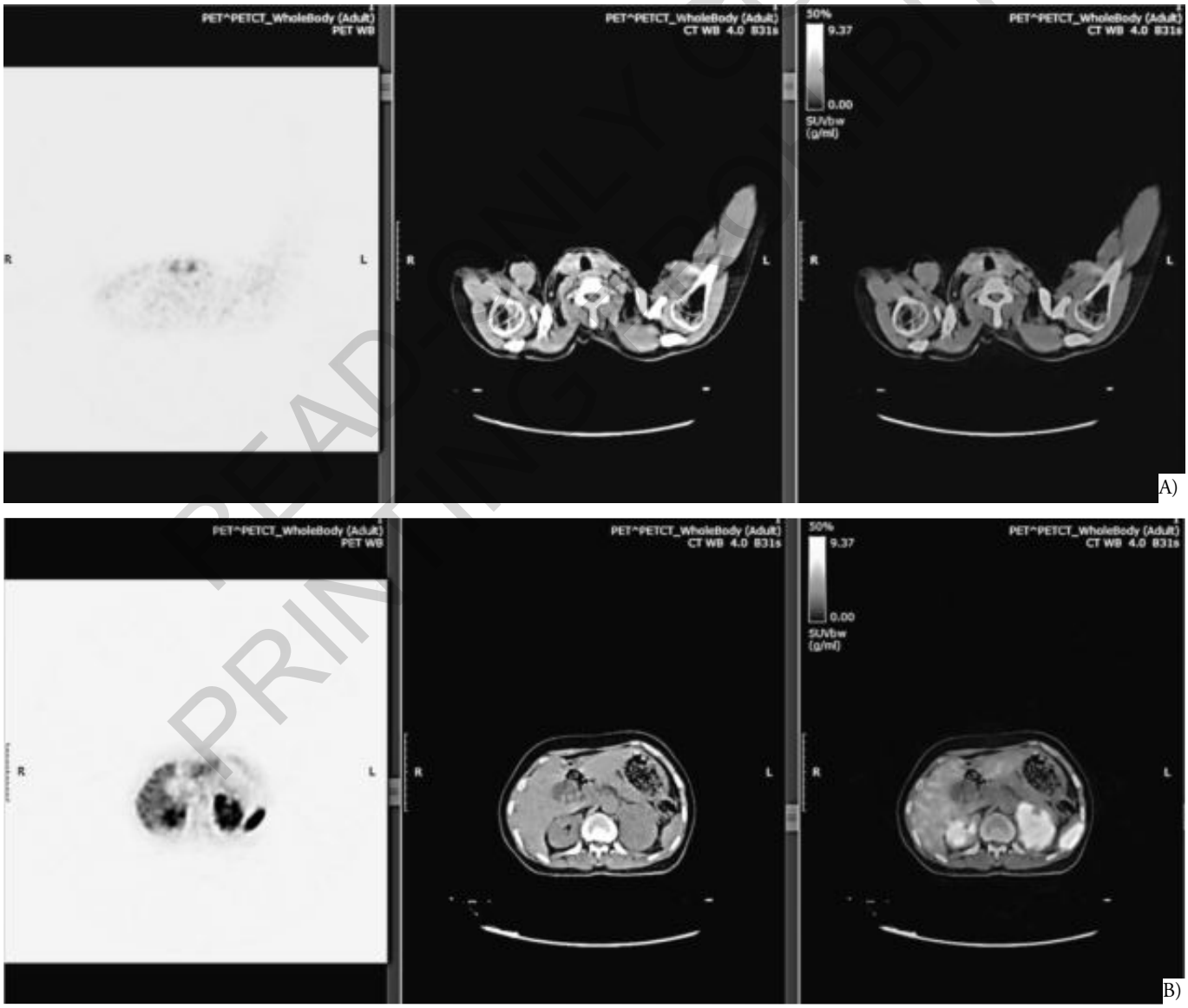

Fig. 1: A) Increased SUVmax (3,3) at left lobe of the thyroid; B Left adrenal mass with a high SUVmax (9,1).

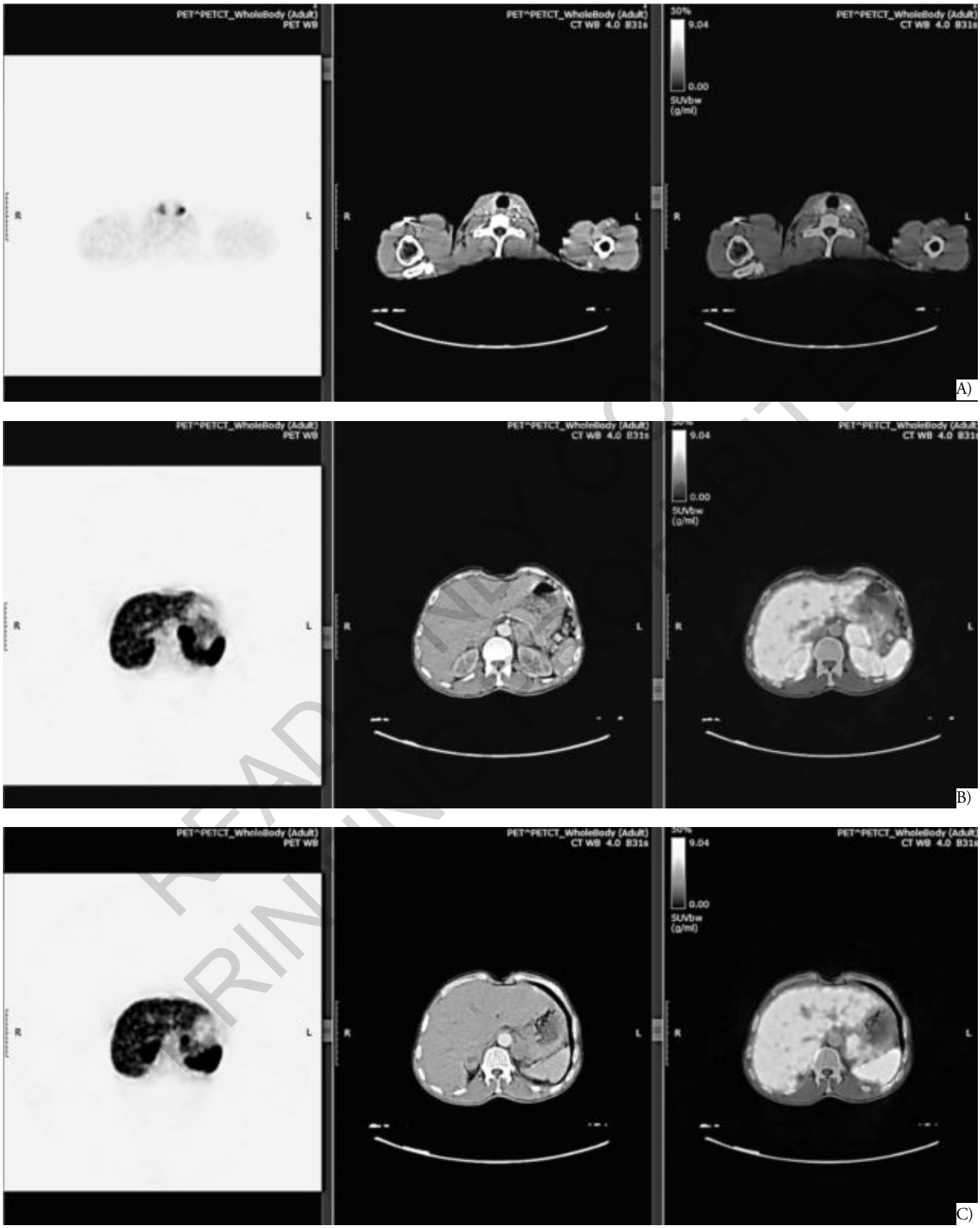

Fig. 2: A) 68Ga-DOTATATE PET/CT imaging showed increased SUVmax (7,7) at the left lobe of the thyroid; B) 68Ga-DOTATATE PET/CT imaging showed left adrenal mass SUVmax: 32,4; C) 68Ga-DOTATATE PET/CT imaging showed right adrenal mass, SU.

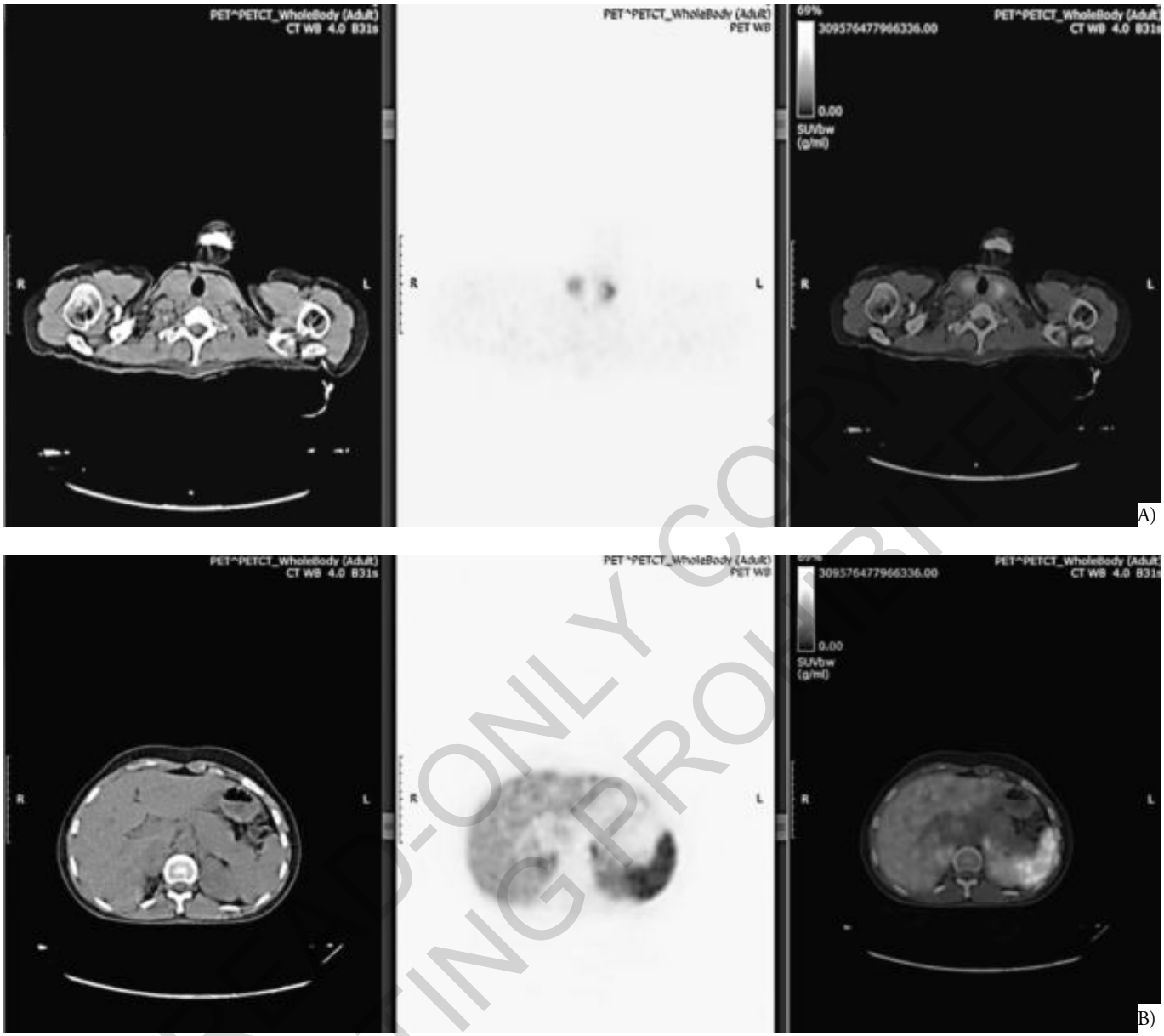

Fig. 3: A) 68Ga-DOTATATE PET/CT imaging showed increased SUVmax at the right and left lobe of the thyroid (left thyroid nodule SUVmax: 19,4, right thyroid nodule SUVmax 21,2); B) 68Ga-DOTATATE PET/CT imaging showed right adrenal mass with a high SUVmax (SUVmax 12,4).

tral lymph nodes. Immunohistochemical examination of thyroidectomy material revealed CEA, chromogranin a, synaptophysin, calcitonin. Patient characteristics are summarized in Table I.

Discussion

This study showed that 68Ga-DOTATATE PET/CT may be used correctly for localization in MEN 2A syndrome. These cases had big adrenal masses and quietly elevated catecholamine degradation products. Both patients had RET oncogene mutation. First case had a thyroid nodule with a 18x10mm at the left lobe of the thyroid and increased calcitonin levels. Second case has also thyroid nodules with an increased calcitonin levels. These findings would indicate the MEN2A syndrome in both patients. MEN2A associated pheochromocytomas may account for less than the 10% of all malignancies reported for sporadic pheochromocytomas [10,11].
Pheochromocytomas often express more than one somatostatin receptor and MTC is the only malignant tumor [12]. The prognosis of MEN2 mainly depends on MTC (medullary thyroid cancer). Cervical lymph node metastasis accompanies 70% of MTC cases and this situation correlates with poor outcome [13]. Owing to their

TABLE I - *Patient characteristics*

	Case 1	Case 2	Case 3
24 hours urine metanephrine (normal range: 52-341µg/24 hour)	21767↑	3762↑	3126↑
24 hours urine normetanefrin (normal range 88-444µg/24 hour)	3369↑	1745↑	1033↑
Plasma calcitonin (normal range: 0-11.5pg/ml)	1181↑	327↑	110.5↑
Adrenal mass(mm)	52x60x54	R:47x32 L:30x26	28x22
Thyroid nodule(mm)	18x10	R:8,3x8,1 L:16x20	n/a
Pathology of adrenal lesion	pheochromocytoma	pheochromocytoma	pheochromocytoma
Pathology of thyroid lesion	medullary thyroid cancer	medullary thyroid cancer	medullary thyroid cancer
Adrenal mass 68Ga-DOTATATEUptake (SUVmax)	9,1	right: 32.4 left: 30,3	12,4
Thyroid nodule 68Ga-DOTATATE (SUVmax)	3,3	7,7	left nodule: 19,4 right nodule: 21,2
Parathyroid adenoma	no	no	yes
68Ga-DOTATATE (SUVmax) parathyroid adenoma	(–)	(–)	2,8

neuroendocrine origin, MTC cells express somatostatin receptors on their surface. In vitro reverse transcriptase polymerase chain reaction (RT-PCR) studies, in MTC cell lines have identified somatostatin receptor 2 (SSTR2) and 5 (SSTR5) as the most frequent subtypes expressed in this tumour [14,15].

In vivo detection of SSTR expression has so far been the molecular basis for tumor imaging with radio labelled somatostatin analogues in SPECT imaging, such as 111In-octreotide. The 68Ga-DOTATATE is a novel PET tracer which consists of DOTA-DPhe1, Tyr3-octreotate (DOTATATE), SSTR2 analogue labelled with 68Ga. The 68Ga-DOTATATE has high affinity for SSTR2 [16], demonstrates fine target to non-target imaging properties and has already shown satisfactory sensitivity in neuroendocrine tumour imaging [17].

In patients with elevated calcitonin levels (>1000 pg/ml), additional imaging studies should be considered to rule out distant (often hepatic) metastases. This should include whole-body CT, bone MRI (whole-body MRI or MRI of spinal and pelvic bone marrow) and bone sintigraphy. The 18F-FDOPA and 18 F-FDG PET/CT may be useful in patients who were suspected to have metastatic disease. In our patients 18 F-FDG PET/CT imaging did not show increased activity both for pheochromocytoma and thyroid nodules. We chose 68Ga-DOTATATE PET/CT as a imagining besides other imagining tecnics (such as ultrasonography, CT or MRI) to show existence of disease and distant metastasis if any. The 68Ga-DOTATATE PET/CT can be an alternative method to show multiple neuroendocrine tumors such as MEN2A.

To our knowledge, this was one of the first attempts to detect and map the entire extent of disease in patients with MEN 2A by the use of the novel PET tracer 68Ga-DOTATATE.

Conclusion

In this study we showed benefits of a new imaging method 68Ga-DOTATATE PET/CT as an alternative method to diagnose evidence of neuroendocrine tumors or their metastasis (if any) in patient with MEN 2A.

As a result new imaging method 68Ga-DOTATATE PET/CT may be an alternative method to diagnose MEN 2A patients. Further studies are needed to confirm our results.

Riassunto

Lo scopo di questo studio è di valutare un nuovo metodo di imaging 68Ga-DOTATATE PET/CT come metodo alternativo per diagnosticare l'evidenza di tumori neuroendocrini o le loro metastasi (se presenti) nel paziente con MEN 2A.

Sono stati studiati prospetticamente tre pazienti (2 donne ed un uomo) di età rispettivamente di 28, 46 e 50 anni, con sindrome MEN 2A sottoposti a scansione PET / TC 68Ga-DOTATATE. Le immagini PET/CT sono

state analizzate con la misurazione del massimo valore di assorbimento standardizzato (SUVmax).
Tutti i pazienti presentavano masse surrenali con aumento dell'assorbimento di 68Ga-DOTATATE (massa surrenale del primo caso SUVmax: 9,1, massa surrenale del secondo caso SUVmax: 32,4 (destra) e 30,3 (sinistra) e terzo caso SUVmax: 12, 4). Tutti i pazienti avevano un carcinoma midollare della tiroide con aumento dell'assorbimento di 68Ga-DOTATATE (primo caso SUVmax: 3,3; secondo caso SUVmax: 7,7 e terzo caso SUVmax: nodulo tiroideo sinistro: 19,4, nodulo tiroideo destro: 21,2. Il terzo caso aveva un adenoma paratiroideo con SUVmax: 2,8.
Si convlude che il nuovo metodo di imaging 68Ga-DOTATATE PET/CT può essere un metodo alternativo per diagnosticare i pazienti MEN 2A. La 68Ga-DOTATATE PET/CT può dare una grande opportunità per rilevare le neoplasie multiple come MEN 2A con una sola sessione di indagine

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